

## Bishomocubane Chemistry. 14. Molecular Mechanics Calculations on Bishomocubyl Systems<sup>1,2</sup>

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Received March 9, 1993\*

Molecular mechanics calculations have been performed on several bishomocubane derivatives in order to better understand their reactivities and properties. Strain energies of the five bishomocubane hydrocarbons, (CH)<sub>8</sub>(CH<sub>2</sub>)<sub>2</sub>, calculated by the MM2(87) method increase in the order 1,4 < 1,3 < 1,3' < 1,2 < 1,1. The values are 73.34, 76.63, 90.14, 93.12, and 112.57 kcal/mol, respectively. The order of the 1,4 and 1,3 isomers is reversed from that of previous calculations using the Allinger 1971 and Engler 1973 force fields. Approximately the same order was found for the corresponding compounds that contained only the cyclobutane portions of these bishomocubanes. The same order was calculated for the *gem*-dimethyl derivatives of 1,4- and 1,3-bishomocubane in contrast to the order found in previous calculations using the Allinger 1971-1972 force field. Calculated strain energies of the *gem*-dimethyldibromo- and *gem*-diphenylmethoxybromo-1,3- and -1,4-bishomocubane ethylene ketals also increase in the order 1,4 < 1,3. Perchloro-1,4-bishomocubane has a lower calculated strain energy than does perchloro-1,3-bishomocubane, 187.17 vs 195.70 kcal/mol. Enthalpies of formation were calculated for *endo*-dicyclopentadiene, two substituted derivatives, and the related 1,3- or 1,4-bishomocubanes. Geometries were calculated for 1,3-bishomocubane, methylene-1,3-bishomocubane, several hydroxy derivatives, and related hydrocarbons. These results add to our understanding of several reactions and properties of these compounds.

### Introduction

Molecular mechanics calculations have been used extensively to predict enthalpies of formation, strain energies, and geometries of organic compounds including some in the bishomocubane series.<sup>1-24</sup> The seeming inconsistency of some of these calculations and the general interest in

these compounds<sup>1,24-31</sup> prompted a further investigation of these calculations and an extension to other derivatives.

### Results and Discussion

The enthalpies of formation and strain energies of the five bishomocubanes 1-5<sup>1,32</sup> as calculated by the MM2(87) program<sup>19,33,34</sup> are given in Figure 1. As expected, all five of these isomers have lower strain energies than that of homocubane (11) or cubane (12) (Figure 1), mainly because of smaller deviations from the normal tetrahedral bond angles for the bishomocubanes. Our calculated strain energies for 2, 11, and 12 agree exactly with values calculated recently by other workers.<sup>20,21</sup>

\* Abstract published in *Advance ACS Abstracts*, September 1, 1993.

(1) Part 13: Dilling, W. L. In *Carbocyclic Cage Compounds: Chemistry and Applications*, Osawa, E.; Yonemitsu, O., Eds.; VCH Publishers: New York, 1992; pp 249-291.

(2) Results presented, in part, at the 205th National Meeting of the American Chemical Society, Denver, CO, March 28-April 2, 1993 (Abstract: Dilling, W. L. *Book of Abstracts*, ORGN 39), the 33rd National Organic Chemistry Symposium, American Chemical Society, Boseman, MT, June 13-17, 1993 (Abstract: Dilling, W. L. *Book of Abstracts*, A-60), and the 206th National Meeting of the American Chemical Society, Chicago, IL, Aug 22-27, 1993 (Abstract: Dilling, W. L. *Book of Abstracts*, ORGN 37).

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1	2	3	4	5
$\Delta H_f$ 44.55	47.85	61.35	65.12	83.78 kcal/mol
SE 73.34	76.63	90.14	93.12	112.57 kcal/mol
				
6	7	8	9	10
$\Delta H_f$ 6.88	26.33	49.45	52.86	84.35 kcal/mol
SE 27.51	51.88	79.91	77.57	108.21 kcal/mol
				
11	12	13	14	
$\Delta H_f$ 95.11	148.85	29.57	34.02 kcal/mol	
SE 118.13	166.12	74.14	78.59 kcal/mol	

Figure 1. Enthalpies of formation and strain energies (SE) calculated by MM2(87).

In carbocyclic systems, four-membered rings are significantly more strained than five- or six-membered rings. Thus, we originally reasoned that one could predict the order of strain energies in the bishomocubanes 1-5 by considering only the four-membered ring portions of these molecules. 1,4-Bishomocubane (1) contains two four-membered rings that are not fused to each other and should be the least strained of the five bishomocubanes. 1,3-Bishomocubane (2) contains two four-membered rings fused to each other and should be the next most strained. Both 1,3' (3) and 1,2-bishomocubane (4) contain three four-membered rings fused to each other, linearly fused in 3 and fused about a single carbon atom in 4. The latter appeared to us to be the more strained. 1,1-Bishomocubane (5) contains four four-membered rings fused to each other and was predicted to be the most strained of the five isomers. Thus, the predicted order of increasing strain energy was  $1 < 2 < 3 < 4 < 5$ , the order actually found by the MM2 calculations.

To test whether the hydrocarbons analogous to 1-5 with the non-four-membered ring portions removed follow the same strain order, we calculated the strain energies of compounds 6-10 (Figure 1). The order is nearly the same; only the tricycloalkanes 8 and 9 are interchanged. The calculated strain energies of these two compounds differ only slightly compared with the range of strain energies for the entire series of compounds 6-10. The calculated minimum energy structures of 8 and 9 are shown in Figure 2. One possible reason for the reversal in relative strain energies of 8 and 9 may be the 2.279 Å interaction of the two endo hydrogen atoms of 8 (two such interactions by symmetry). The closest nongeminal, nonvicinal, hydrogen-hydrogen distance in 9 is 2.673 Å (three such interactions by symmetry). These types of hydrogen-hydrogen interactions are absent in 3 and 4 and may account for the reversed order. Interestingly, the strain energies of 6-10 are all  $\sim 26$ -27 kcal/mol per four-membered ring.<sup>35</sup>

In comparing the strain energy orders of 1-5 and 6-10 possibly twice the strain energy of cyclobutane (6) should

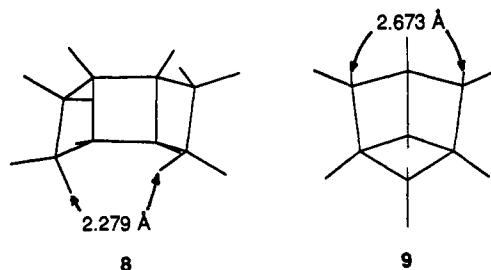


Figure 2. MM2-calculated structures of tricyclic hydrocarbons 8 and 9.

be used because 1 has two four-membered rings. If this is done, compounds 1 and 2 are not in the same order as  $2 \times 6$  (55.02 kcal/mol) and 7. However, again the noncage series has hydrogen-hydrogen interaction differences, two more cis vicinal interactions in  $2 \times 6$  than in 7, that are not present in the bishomocubane series.

The above discussion does not take into account the other non-four-membered ring related interactions present in these molecules. The MM2 calculation does take into account all significant aspects of strain in these molecules, not just that attributable to the arrangement of the four-membered rings.

Godleski and co-workers<sup>9</sup> reported enthalpies of formation of the bishomocubanes 1 and 2 calculated by the Allinger 1971 and Engler 1973 force fields. The values for the 1,4 isomer 1 were higher than for the 1,3 isomer 2 (49.86 and 48.34 kcal/mol, respectively, for the Engler force field; 55.03 and 52.19 kcal/mol, respectively, for the Allinger force field). Ōsawa and co-workers<sup>7</sup> calculated enthalpies of formation and strain energies for the *gem*-dimethyl derivatives, 13 and 14, by using the Allinger 1971-1972 force field. They also found higher values for the 1,4 isomer 13 (39.35 and 82.03 kcal/mol, respectively) than for the 1,3 isomer 14 (37.63 and 80.31 kcal/mol, respectively). These relative values are reversed from the results of the present calculations, which employed the MM2(87) program (Figure 1). We find both 1,3-bishomocubanes, 2 and 14, to have higher enthalpies of formation and strain energies than the corresponding 1,4-bishomocubanes, 1 and 13, respectively. The differences in these earlier workers' and our results apparently were caused by the different parameters used in the various programs. Earlier, Schleyer and co-workers reported a higher calculated strain energy for 1,1,4-trishomocubane (one methylene bridge and one ethano bridge) than for 1,1,3-trishomocubane.<sup>36</sup> Calculated strain energies of the other trishomocubanes paralleled our results on the bishomocubanes.<sup>36</sup>

The results of acetolyses of secondary sulfonate ester derivatives 15 and 26-29 of the bishomocubanes 1-5, summarized in Figure 3,<sup>32,37,38</sup> are in general agreement with expectations based on the calculated strain energies of 1-5. The most strained ester 15 gave products, rationalized by a series of 1,2-alkyl shifts of carbocations (Figure 3), representing all five bishomocubyl systems.<sup>37</sup> All of the other esters 26-29 gave products with lower or nearly the same strain energies as the starting ester.<sup>32,37,38</sup> The relative rates of these acetolyses (25 °C, Figure 3) also agree in general with expectations that the fastest rates

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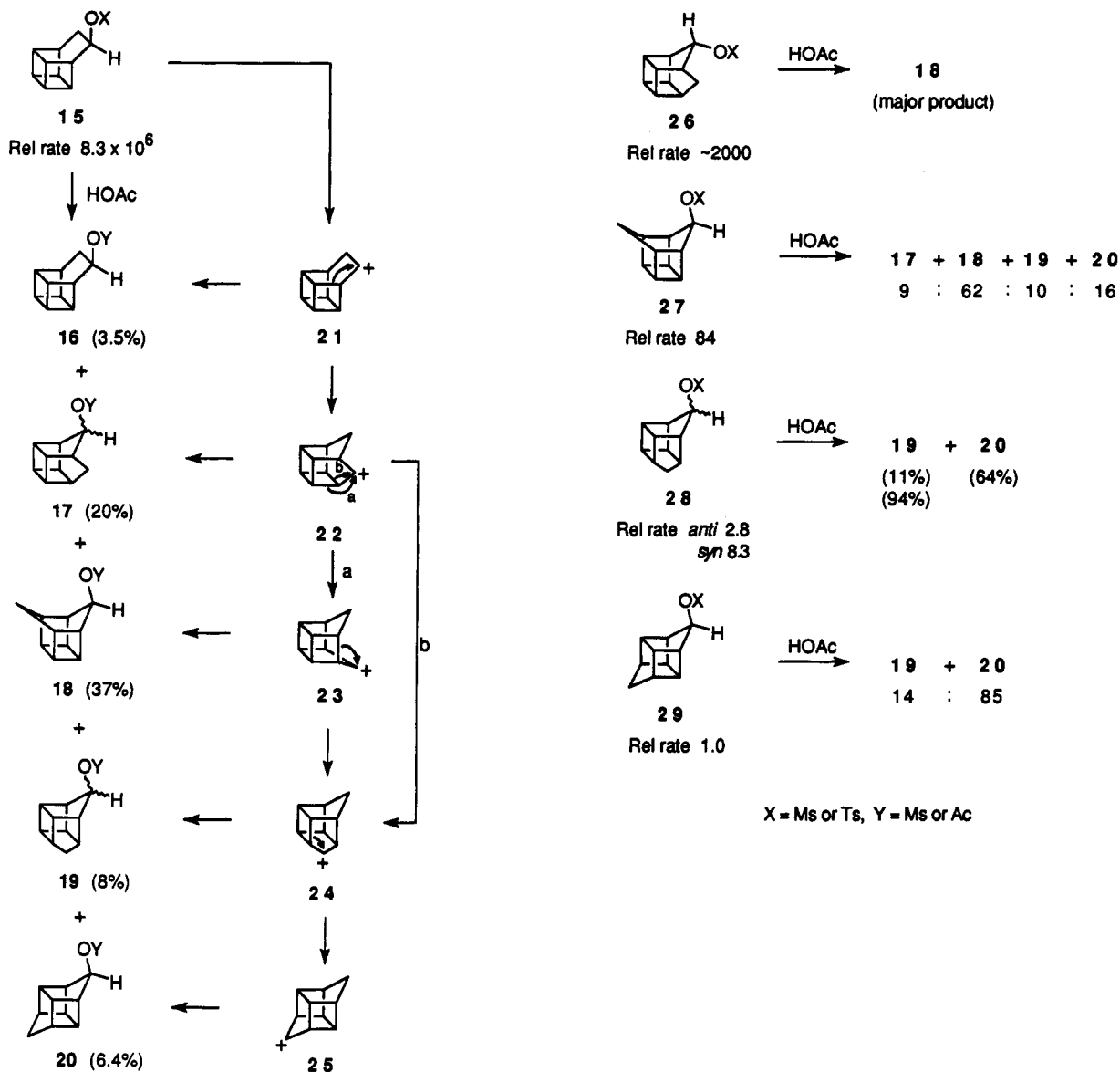


Figure 3. Rearrangements of bishomocubyl cations on acetolyses of sulfonate esters.

would occur for those esters in which the most strain can be relieved in the transition state.

Ring expansion reactions of homocubylcarbinyl systems 30 and 37 (Figures 4 and 5) gave 1,3-bishomocubyl products 31, 32, and 38 rather than the 1,4 isomers 33 and 39, respectively.<sup>39,40</sup> MM2 calculations on 30, 32, 33 (Figure 4), and 37-39 (Figure 5) gave the same order of strain energies as noted above for the hydrocarbons 11, 2, and 1 (and 14 and 13). Thus, the less stable (by MM2) 1,3 isomers are formed rather than the more stable 1,4 isomers. The earlier explanation of a probable higher steric strain for the 1,4 isomer 33 compared to that of the 1,3 isomer 32<sup>7</sup> is probably incorrect. Calculations on the specific compounds, 33 and 32 (Figure 4), show the reversed order of strain energies.

The explanation of more relief of strain in the homocubyl system by cleaving one of the a bonds (34 and 40, Figures 4 and 5, respectively) than by cleaving the b bond<sup>39</sup> may be correct. The calculated enthalpies of formation and

strain energies of the hydrocarbons 43 and 44 resulting from cleavage of the a and b bonds, respectively, of homocubane (11) are shown in Figure 6. The values calculated by the Allinger 1971-1972 force field (46.07 and 74.57 kcal/mol, respectively, for 43 and 56.23 and 84.73 kcal/mol, respectively, for 44<sup>7</sup>) were in the same order as calculated by the MM2(87) program, although the differences were much smaller from the latter calculation. The difference in the bond strain energies of 11 (Figure 6) is only  $\sim 1$  kcal/mol.<sup>7</sup>

The symmetrical hydrocarbon 44 has a closer calculated nonbonded hydrogen-hydrogen interaction, 2.082 Å, than does 43, 2.217 Å (Figure 7). These repulsions are not present in a homocubyl system undergoing bond cleavage. Thus, 43 and 44 may not be good models of the bond-cleaved systems. The diketones 45 and 46 (Figure 6) do not have these close hydrogen interactions, but the relative strain energies are in the same order. The calculated difference in strain energies is much larger between the diketones than between the hydrocarbons.

A recent report of similar reactions of homocubylcarbinyl and cubylidcarbinyl systems indicated that mixtures of 1,3- and 1,4-bishomocubyl products were formed, with

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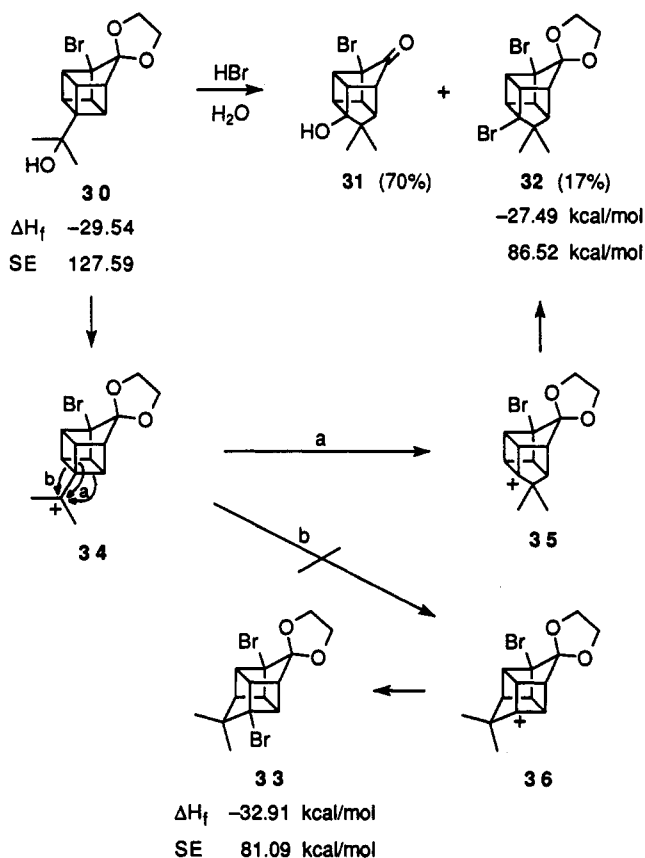


Figure 4. Enthalpies of formation and strain energies of homocubylcarbinol 30 and possible ring-expansion products.

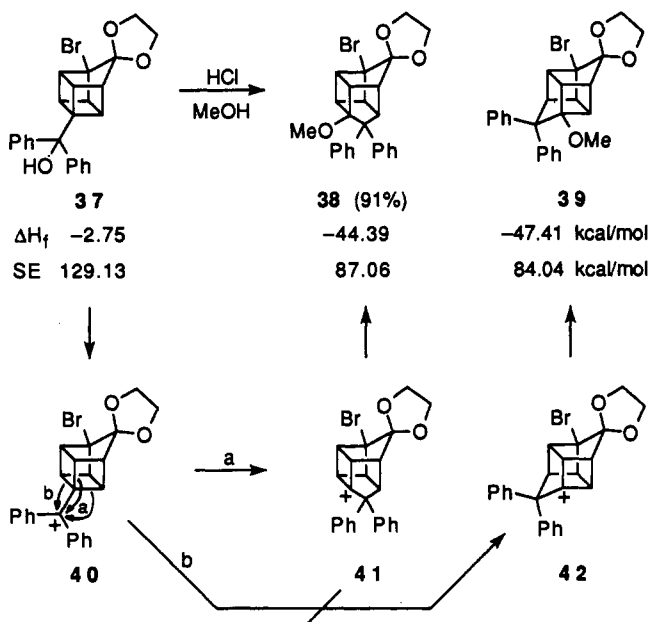


Figure 5. Enthalpies of formation and strain energies of homocubylcarbinol 37 and possible ring-expansion products.

larger amounts of the 1,4 isomer being formed from more highly stabilized cations related to 40.<sup>24</sup> A consistent explanation for all the above results involves kinetic control in reactions of the less stable homocubylcarbinyl cations to give the less stable 1,3-bishomocubyl isomers by cleaving the more strained a bonds and thermodynamic control in reactions of the more stable cations to give the more stable 1,4 isomers by cleaving the b bond.

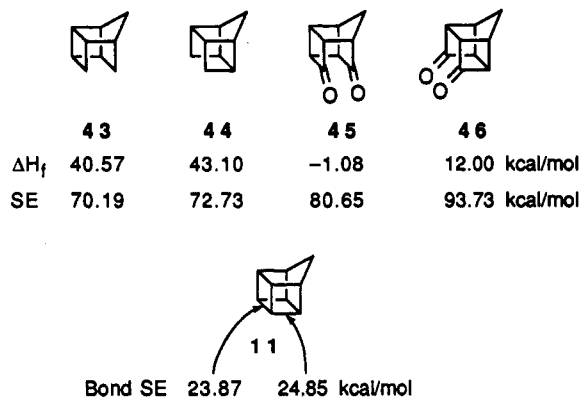


Figure 6. Enthalpies of formation and strain energies of model secohomocubanes and bond strain energies of homocubane (11).

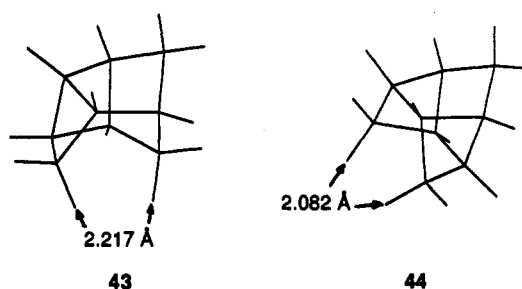


Figure 7. MM2-calculated structures of secohomocubanes 43 and 44.

Perchloro-*endo*-dicyclopentadiene (47) gave perchloro-1,4-bishomocubane (48) (mirex) on treatment with  $AlCl_3$ .<sup>41</sup> If a cationic rearrangement via 50-52 is responsible for this transformation,<sup>41</sup> the possibility exists for the formation of perchloro-1,3-bishomocubane (49) as well (Figure 8). MM2 calculations on 47-49 explain the preferential formation of 48. The very high calculated strain energies of 47-49 compared to the values for the corresponding hydrocarbons is interesting in light of the high stability of the chlorocarbons.

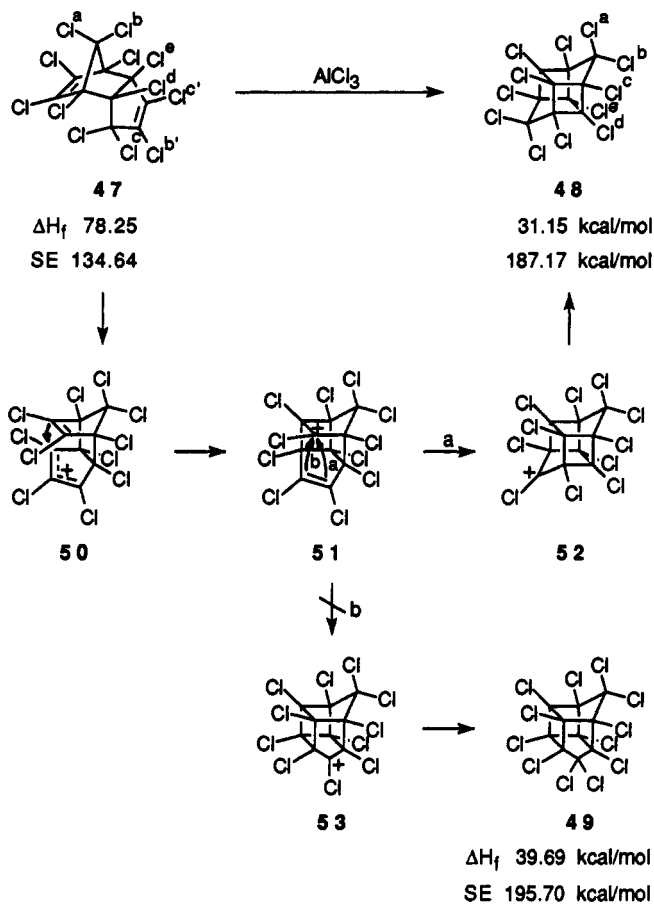
An attempt to prepare the 1,3 perchlorocarbon 49 by reaction of the diketone 54 with  $PCl_5$  gave the 1,4 isomer 48<sup>42</sup> (Figure 9). A likely mechanism for this reaction via cations 55 and 56 would explain this transformation.<sup>32</sup> The rearrangement of the 1,3-bishomocubyl system to the 1,4 isomer is entirely reasonable in light of the MM2 calculations.

The calculated enthalpy change for the conversion of the perchlorodiene 47 to the cage isomer 48 (Figure 8) is exothermic by 47.10 kcal/mol. This exothermicity is in qualitative agreement with the ease of this process.<sup>41</sup> In contrast, the calculated enthalpy change for the hypothetical analogous conversion of the corresponding hydrocarbon (57  $\rightarrow$  1) is nearly thermoneutral. At least two factors may contribute to the greater exothermicity of the chlorinated system (47  $\rightarrow$  48) than that of the hydrocarbon system (57  $\rightarrow$  1). One is the differential effect of chlorine substituents on the enthalpy of formation of alkenes and cyclobutanes. Calculations using Benson's group values<sup>43</sup> indicate greater exothermicities for the conversion of chloroalkenes to chlorocyclobutanes than for the conver-

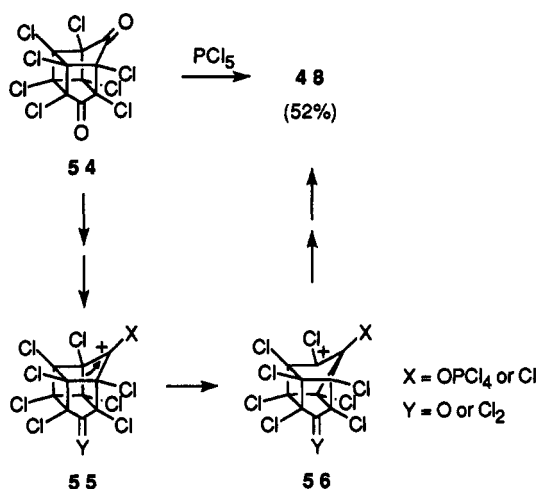
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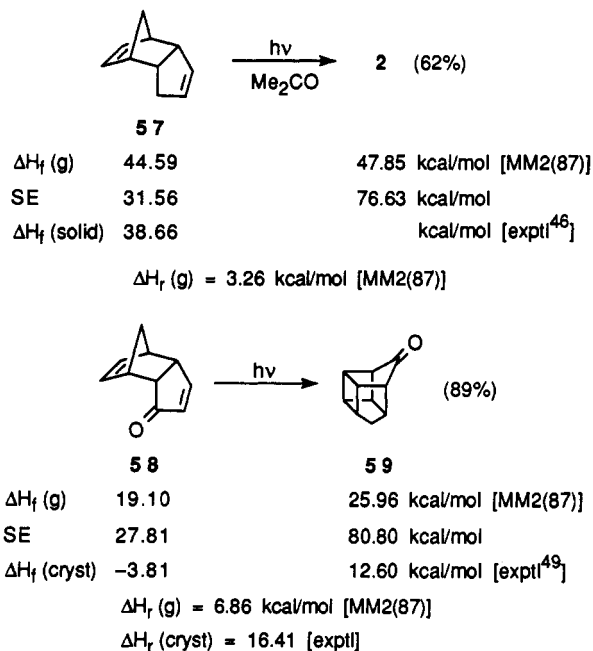


**Figure 8.** Enthalpies of formation and strain energies of perchloro-endo-dicyclopentadiene (47) and possible ring-closure products.



**Figure 9.** Rearrangement of perchloro-1,3-bishomocubanedione (54) on reaction with  $\text{PCl}_5$ .

sion of hydrocarbon alkenes to cyclobutanes. A second factor may be relief of steric compression of chlorine atoms in the diene 47 on conversion to the 1,4-bishomocubane 48. Of the various types of close Cl...Cl interactions in 48 (Figure 8), the following interatomic distances, calculated by MM2, in 47 show the greatest increase on conversion to 48:  $\text{Cl}^a\cdots\text{Cl}^b$ , 2.914  $\rightarrow$  2.968 Å;  $\text{Cl}^b\cdots\text{Cl}^c$ , 3.342  $\rightarrow$  3.511 Å ( $\text{Cl}^b\cdots\text{Cl}^e$ );  $\text{Cl}^b\cdots\text{Cl}^d$ , 3.110  $\rightarrow$  3.746 Å;  $\text{Cl}^c\cdots\text{Cl}^d$ , 3.058  $\rightarrow$  3.357 Å;  $\text{Cl}^d\cdots\text{Cl}^e$ , 3.169  $\rightarrow$  3.247 Å. Other Cl...Cl interactions in 47 are also relieved on conversion to 48. These



**Figure 10.** Enthalpies of formation and strain energies of endo-dicyclopentadiene (57), the ketone 58, and their photochemical ring-closure products 2 and 59.

are significant changes in light of the 1.8 Å van der Waal's radius of chlorine.<sup>44</sup>

The known photochemical transformation of the diene 57 to the 1,3-bishomocubyl isomer 2<sup>45-47</sup> is calculated to be endothermic by 3.26 kcal/mol (Figure 10), a lower value than the 9.76 kcal/mol calculated previously using the Allinger 1971-1972 force field.<sup>5</sup> A slightly larger endothermicity, 6.86 kcal/mol, is calculated for the related transformation of the dienone 58<sup>49,50</sup> (Figure 10). This calculated gas-phase value is somewhat lower than the 16.41 kcal/mol crystal-phase value derived from the experimental enthalpies of formation of the reactant 58 and product 59.<sup>51</sup> Enthalpies of vaporization for 58 and 59 would be required for us to make a direct comparison.

Metal hydride reductions<sup>32,50,52</sup> of and additions of organometallic reagents<sup>49</sup> to 1,3-bishomocubane 59 (Figure 11) indicate that the reagents attack the bridge carbon atom preferentially from the anti side. Peracid epoxidation of methylene-1,3-bishomocubane (64) (Figure 12) also shows a slight preference for anti attack.<sup>53,54</sup> MM2 calculations show that one of the carbon-hydrogen internuclear distances, indicated in Figure 13, in 59 and 64 is shorter than the other three indicated distances. One

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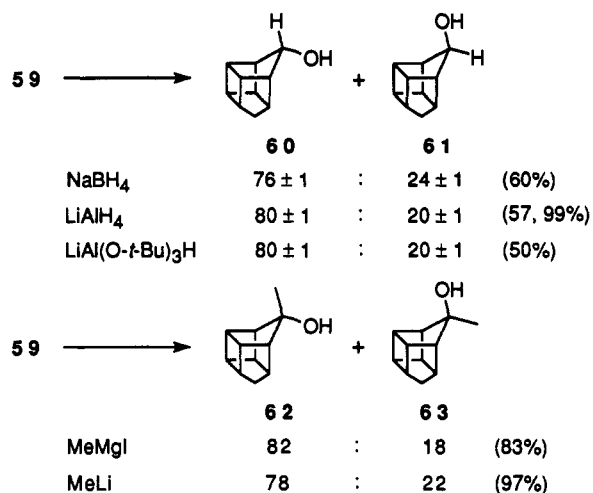
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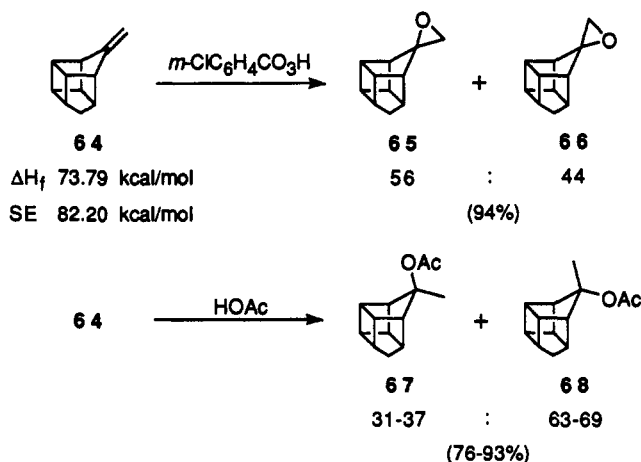
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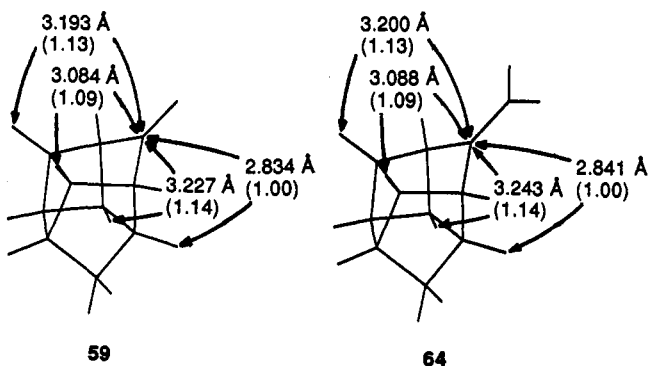
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**Figure 11.** Stereochemistry of hydride reductions of and addition of organometallic reagents to 1,3-bishomocubane (59).

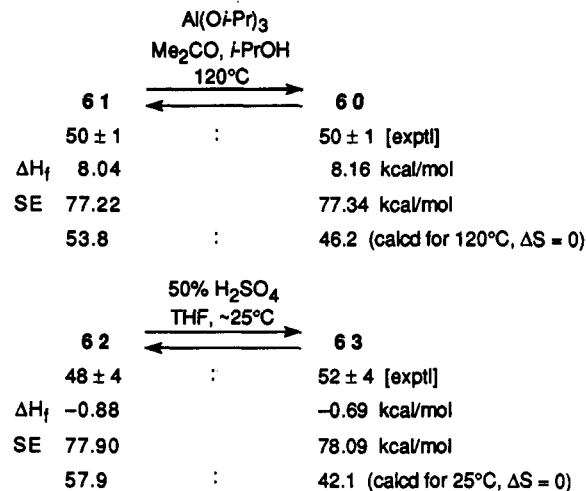


**Figure 12.** Enthalpy of formation and strain energy of olefin 64 and stereochemistry of its epoxidation and HOAc additions.

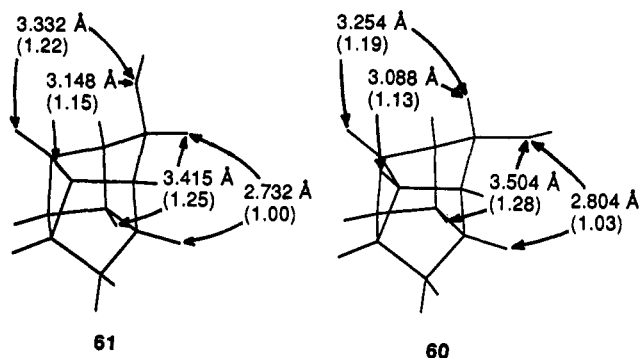


**Figure 13.** MM2-calculated structures of 1,3-bishomocubane (59) and methylene-1,3-bishomocubane (64) (relative distances in parentheses).

explanation for the selectivity exhibited in these reactions is the steric effect of this close hydrogen atom in partially blocking the syn side of the bridge carbon atom that is attacked. The lower selectivity in the epoxidation could result from an attack of the peracid near the center of the carbon-carbon double bond while the reactions at the carbonyl group occur on its carbon atom, nearer the close hydrogen atom. The predominance of the syn acetate 68 over the anti epimer 67 in the addition of acetic acid to 64 under various conditions<sup>53,54</sup> may result from prefer-



**Figure 14.** Enthalpies of formation and strain energies of 1,3-bishomocubanol 60-61 and 62-63 and their equilibrations.



**Figure 15.** MM2-calculated structures of *anti*- (61) and *syn*-1,3-bishomocubanol (60) (relative distances in parentheses).

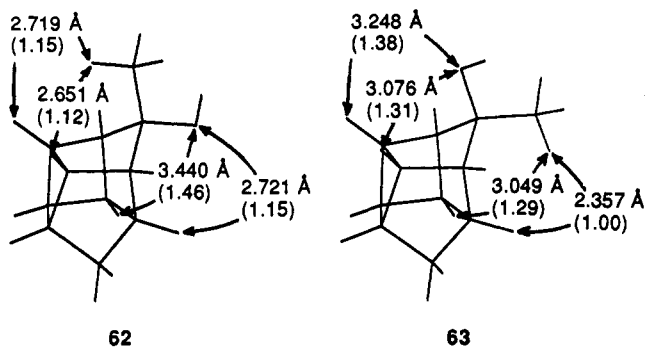
ential bridging of the intermediate cation on the *anti* side, leaving the *syn* side more open to attack by acetate.

Equilibration of the secondary alcohols 60 and 61 gave nearly equal amounts of the two epimers<sup>52</sup> (Figure 14). MM2 calculations indicate that the *syn* isomer 60 is slightly more strained than the *anti* isomer 61. This calculated enthalpy difference (gas phase) translates into a 46.2:53.8 equilibrium mixture in favor of the *anti* alcohol 61 at 120 °C if  $\Delta S$  is negligible.<sup>55</sup> The closer O...H distance in 60 compared to 61, indicated in Figure 15, may explain the difference in their calculated stabilities.

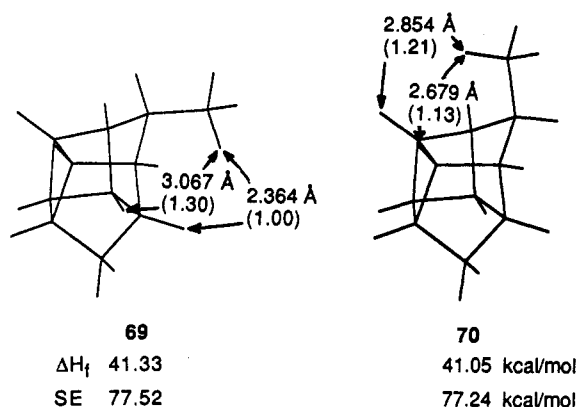
Likewise, equilibration of the tertiary alcohols 62 and 63 gave nearly equal amounts of the two isomers<sup>53</sup> (Figure 14). The calculated enthalpy difference leads to a predicted equilibrium composition of 57.9:42.1 at 25 °C in favor of the *syn* alcohol 62. The lowest energy conformation of 63 has the shortest interatomic distance of those shown in Figure 16 and may explain the calculated preference for the *syn* alcohol 62. The experimental results, although not very precise, do not reflect this preference.

Calculated enthalpies of formation and strain energies of *syn*- 69 and *anti*-methyl-1,3-bishomocubane 70 are shown in Figure 17. Again, one of the C...H distances in the *syn* methyl isomer 69 is shorter than corresponding distances in the *anti* epimer 70. Not unexpectedly, the difference in enthalpies of formation between the *syn* and

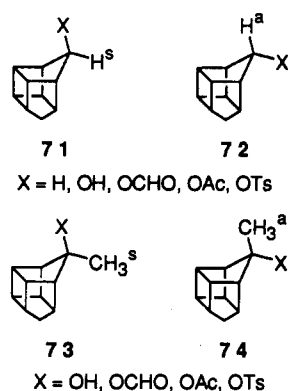
(55) See ref 9 for a discussion of the relevance of  $\Delta S$  in these calculations. The closely related structures discussed here should minimize the importance of  $\Delta S$  in these calculations.



**Figure 16.** MM2-calculated structures of methyl-*syn*- (62) and methyl-*anti*-1,3-bishomocubanol (63) (relative distances in parentheses).



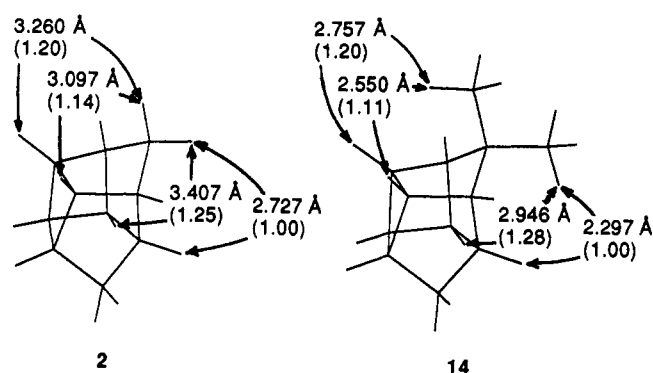
**Figure 17.** MM2-calculated structures of *syn*- (69) and *anti*-methyl-1,3-bishomocubane (70) (relative distances in parentheses).



**Figure 18.** *Syn* (s) and *anti* (a) protons on 1,3-bishomocubyl derivatives.

*anti* methyl isomers 69 and 70, 0.28 kcal/mol, is larger than the corresponding difference in the secondary alcohols 60 and 61, 0.12 kcal/mol. Thus, the methyl group has a stronger preference for the *anti* position than does the hydroxyl group. When both substituents are present, as in 62 and 63, the preference of the methyl group is greatest, and the most stable isomer is the *anti* methyl, *syn* hydroxyl isomer 62, by 0.19 kcal/mol.

Proton NMR spectra of several *syn* and *anti* pairs of 1,3-bishomocubyl derivatives (Figure 18) show that the chemical shifts of protons,  $H^s$ , on the *syn* side of the methylene bridge are shifted downfield relative to those,  $H^a$ , on the *anti* side.<sup>56</sup> The chemical shifts of methyl



**Figure 19.** MM2-calculated structures of 1,3-bishomocubane (2) and *gem*-dimethyl derivative 14.

protons in 73 and 74 differ more,  $\delta_{H^s} - \delta_{H^a} = 0.29$ – $0.32$  ppm, than do those of the secondary derivatives 71 and 72,  $\delta_{H^s} - \delta_{H^a} = 0.23$ – $0.29$  ppm. Calculated interatomic distances (Figures 15, 16, 19) of the lowest energy conformations agree with our earlier suggestion that the chemical shift differences may be caused by greater steric compression of the *syn* protons than of the *anti* protons.<sup>56</sup> In all examples the *syn* protons are nearer one of the indicated tertiary protons than are the *anti* protons. The *syn* methyl proton of 14 is nearer to the indicated proton, 2.297 Å, than is the *syn* methylene proton of 2, 2.727 Å (Figure 19). This proximity difference may account for the greater shift difference in the methyl derivatives 73 and 74 than in the secondary derivatives 71 and 72. The same trend is noted in the distances shown in Figures 15 and 16. The relative distances (1.00, 1.17, 1.18, 1.23) estimated with ball and spring models of 2<sup>56</sup> were in the same order and nearly the same magnitude as those (1.00, 1.14, 1.20, 1.25) calculated with the MM2 program.

## Conclusions

MM2(87) calculations indicate that the bishomocubanes increase in strain energy in the order  $1,4 < 1,3 < 1,3' < 1,2 < 1,1$ . This order is approximately the same as that calculated for the analogous set of compounds that contain only the four-membered ring portions of these compounds. These results are consistent with the reactivity of several derivatives of the bishomocubanes. The stereochemistry of several addition reactions of 1,3-bishomocubane and methylene-1,3-bishomocubane are consistent with the calculated geometry of these compounds. The calculated stabilities of *syn* and *anti* isomers of 1,3-bishomocubanol indicate that the isomers with the closer intramolecular interactions between the methylene bridge *syn* substituents and the  $\gamma$  tertiary hydrogen atoms have the higher strain energies. Proton NMR chemical shifts agree qualitatively with calculated geometries that show closer intramolecular interactions of methylene bridge substituents on the *syn* side than on the *anti* side.

**Supplementary Material Available:** Figures (stick, ball and stick, and CPK space-filling) that show the calculated structures of compounds 1-14, 30, 32-33, 37-39, 43-49, 57-64, and 69-70 (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.