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## Conformations of large cycloalkanes: Cyclooctadecane, cyclononadecane and cycloicosane

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### SUMMARY

The conformations of cyclooctadecane, cyclononadecane, and cycloicosane were generated by a stochastic program that works in conjunction with MM2. The shapes of the rings are analyzed in terms of previous work by Dale and others, and in terms of distributions of energies, torsion angle distributions, and torsion angle sequences. A new shape element called the 'nick' has been discovered, and it seems to be increasingly important with 18-membered and larger rings. Previously suggested relationships between ring size and energy distribution were observed, and a geometrical explanation is provided for the relative distributions of stable conformations in 16-, 18-, and 20-membered rings.

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### INTRODUCTION

Many compounds contain large rings; they include (inter alia) natural products such as macrocyclic antibiotics, cyclodextrins, cyclic peptides, and synthetic compounds such as crown ethers, cryptands and catenanes. These large rings are often very flexible, and show complex conformational behavior. Since the physical, chemical and biological behavior of flexible compounds is strongly determined by the conformational behavior, it is of obvious interest to be able to predict the conformational behavior of such molecules. In other papers we have reported the use of the WIZARD [1] technique to exhaustively model the conformations of flexible compounds. WIZARD uses prior axioms of chemistry to predict the conformational behavior of new molecules. Incumbent in the procedure is the need for structural axioms which contain Cartesian coordinate templates for each of the stable conformations for various ring sizes. Thus it is important for WIZARD to have an exhaustive list of conformations (within some energy range) for each ring, and a good understanding of how structural modifications can affect their conformational behavior.

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These templates can be obtained from a number of different sources; from an experimental database such as the Cambridge Structural Database (CSD), or from search techniques based on existing numerical programs (MM2, MOPAC, etc.). Databases such as the CSD may not yield all the conformations for a given ring. Sometimes this is due to experimental difficulties. Large rings (16 members and above) often have numerous conformations which are nearly as stable as the global minimum. Because of this they are either liquid at room temperature or form disordered crystals. Atoms in these molecules retain a large amplitude oscillatory motion above the mean position, further complicating the electron density maps obtained in the X-ray analysis [2,3]. Since the number of representative compounds containing such large rings found in the CSD is often smaller than the total number of stable conformations, this means that some conformations will not be represented.

On the other hand, template generation using torsional angle driving or Monte Carlo techniques and molecular mechanics can be exceedingly time consuming. This is especially true if a complete search of the conformational space to find *all* of the minimum energy structures within a broad energy range is desired. However, if the conformations are to be used as axioms for analogical reasoning then this time factor is offset by the fact that such an exhaustive analysis only needs to be performed once for each cycloalkane. WIZARD itself can be used to generate new templates for cycloalkenes and other related ring systems based on the analogy with the existing templates. These suggestions are then refined using a molecular mechanics program to yield the corresponding energy-minimized geometries. In this paper we report the conformations of cyclooctadecane, cyclononadecane and cycloicosane rings obtained using such a Monte Carlo technique.

Unlike previously reported methods the search was not limited to those conformations within 3 kcal/mol of the lowest energy conformation. This is due to the fact that the analogical construction process used by WIZARD can drastically alter the relative stabilities of conformations. For example, Dale [4] has shown how the possible conformations of 18-crown-6 can be built by converting the appropriate  $-\text{CH}_2$ -groups to ether linkages in selected conformations of cyclooctadecane. In most of the low-energy conformations of cyclooctadecane the hydrogens do not show significant amounts of transannular strain, and this modification would not change the strain energy by very much. However, crown conformation cyclooctadecane contains nearly 3.5 kcal/mol of such transannular strain, almost all of which would be eliminated when the hydrogens were replaced by oxygen lone pairs. If the library contained only those conformations which were within 3 kcal/mol of the lowest energy conformation, WIZARD would be incapable of predicting the correct conformation of 18-crown-6. Dale has also shown how some other substitutions will not drastically effect the basic geometry of the ring skeleton.

## THEORY

Several approaches have been used for the qualitative and quantitative conformational analysis of large rings. Many of these approaches have been aimed at the analysis of even-membered rings that can be superimposed on a diamond lattice. It was recognized quite early [5] that the diamond lattice is a unique way of arranging a carbon skeleton with ideal carbon-carbon lengths (1.54 Å), bond angles (109.5°) and dihedral angles (180° and  $\pm 60^\circ$ ). Thus, those rings that can be superimposed on a diamond lattice should be low-energy conformations. This premise led Smith [6,7] to

use the diamond lattice approach for examination of the conformations of chain polymers and cycloalkanes. Later, Saunders [8] used a diamond lattice approach to predict conformations for cycloalkanes and Uiterwijk et al. [9] used several different diamond lattice algorithms to predict the conformations of cycloalkanes and crown ethers. Naturally, conformations that do not lie on the diamond lattice will not be found with this approach. This includes various strained conformations of even-membered rings, and all conformations of odd-membered rings.

Dale [10–13] proposed a semi-qualitative method of predicting conformations of small and medium cycloalkanes which did not depend on the diamond lattice. This technique was used to generate many low-energy conformations of rings up to cyclohexadecane. Strain energies of these rings were estimated based on values extracted from a calculated energy curve of butane. Although the structures proposed by Dale are quite reasonable, the system has several major problems; a minor problem is that the energies predicted by Dale are only within 20% of the energies calculated by the molecular mechanics method. This semi-quantitative approach does not yield a complete set of conformers. The system is not canonical – a single Dale representation can often correspond to several different conformations. And finally, there is no algorithm one can follow to convert a given Dale representation into a set of Cartesian coordinates. However, Dale's nomenclature is still the best system for describing the conformations of large rings, and the value of Dale's work should not be underestimated.

Computer programs which use the principles of molecular mechanics are being extensively used for conformational and stereochemical analysis [14,15]. However, it is well recognized that an exhaustive conformational analysis of flexible molecules using molecular mechanics with torsion angle driver technique poses several problems [15]. One problem is the large search space involved. For example, a dihedral driving method has been used to independently rotate each bond in a molecule by a very small angle. The structure obtained after each rotation is then minimized. This method is rather impractical and extremely time consuming for large molecules [16]. For example, consider a molecule (cycloicosane) in which 20 internal degrees of freedom (e.g., dihedral angles) are allowed to vary. If only 5 points are sampled for each dihedral angle one still obtains  $5^{20}$  ( $\sim 10^{14}$ ) possible structures. Even if the energy of each conformation can be calculated in 1 microsecond it would still require over 3 years to complete this search. For small- and medium-sized molecules this technique can be quite useful. Lipton and Still [17] used an internal coordinate tree search approach to find conformational minima for small- and medium-sized molecules. They reduced the  $3N-6$  degrees of internal freedom to  $N-3$  by restricting the sampling to torsion angles alone. Each degree of freedom is then partitioned into a number of partitions and then the conformational space is searched by choosing one point from within each partition. Several distance tests and other heuristics were employed to eliminate unreasonable structures. Chemically reasonable starting geometries were generated and later minimized using a molecular mechanics approach. This approach worked quite well for molecules ranging from *n*-pentane to cyclodecane, but later studies with cycloheptadecane showed that this method was not as efficient as the one that employed stochastic variation of internal coordinates followed by energy minimization.

It is therefore clear that while the systematic searches described above can provide a guaranteed coverage of the entire conformational space, they may not be the ideal choice in the case of very large cycloalkanes. These shortcomings have led to the development of stochastic methods. The general algorithm for a successful stochastic method published by Saunders et al. [18–21] is as

follows: First an arbitrary structure is obtained or generated. Then the geometry of the molecule is perturbed by changing the coordinates of every atom by a random amount in a random direction. This is followed by a pre-screen step in which the geometry of the perturbed structure is checked using a two-body force field method. Reasonable conformations retained after this pre-screen are minimized using molecular mechanics. Lipton and Still [22] published another approach utilizing internal coordinates. In this method small perturbations are made to each torsional angle in a chain of equal length to the desired ring. If the ends of the chain are within a designated ring closure distance (0.5–3.5 Å) it is then further screened by examining high-energy non-bonded contacts. A limited molecular mechanics minimization is then used to further screen the conformations, and only those conformations that are within a reasonable energy are completely optimized. A final step in either of these minimizations is the comparison of a newly generated conformer with the previously generated conformations and elimination of duplicates.

Molecular dynamics, distance geometry and statistical mechanics method were applied to the conformational analysis of cycloheptadecane [21]. However, this paper reports that these methods were found to be less effective compared to the stochastic search methods. When a stochastic method is applied there is no conclusive evidence that the conformational search is indeed complete. Saunders [19] has suggested that a probabilistic estimate of completion based on multiple detection of low-energy conformations is feasible. However, this remains only an estimate and may be subject to error.

## EXPERIMENTAL

In order to obtain the conformations of medium and large cycloalkanes we have implemented a Monte Carlo algorithm in a program called MMONTOR. The general algorithm is similar to one reported by Saunders et al. [18–21] but the details are sufficiently different to warrant some discussion. The search starts with one or more reasonable conformations of the cycloalkane. Each iteration begins by randomly selecting a previously discovered conformation whose strain is less than a random cutoff value relative to the most stable conformation discovered so far. The cutoff value is obtained via the formula  $10.0 * \text{ran} * \text{ran}$ , where *ran* is a random number from 0.0 to 1.0. Thus the cutoff energy ranges between 0.0 kcal/mol to 10.0 kcal/mol, with an average of 2.5 kcal/mol. A random number of perturbations are then applied to the molecule. The number of perturbations is chosen by the formula  $\text{int}(40 * \text{ran} * \text{ran}) + 1$ , which gives an integral number from 1 to 41, with an average of 10. The atoms to be perturbed are randomly selected from all of the atoms, including the hydrogen atoms. If a carbon atom is selected the attached hydrogen atoms are carried with it, although they may be independently perturbed either before or after the carbon is perturbed. The distance that the atom is moved is randomly generated, and linearly varies from +3.5 Å to –3.5 Å, and the direction is randomly chosen among the three Cartesian axes. Since the same atom may be chosen numerous times it may be moved along more than one axis before minimization commences.

This *selective perturbation* of atoms is distinct from the *simultaneous general kick* applied to all the atoms of the molecule as described by Saunders. The technique of selective perturbation is supported by Dale's preliminary work on conformational inversion in medium rings. Dale suggests that due to the highly symmetrical nature of these systems, the least expensive conformational changes are localized and consist of elementary processes which are equivalent to the

migration of gauche bonds in anti surroundings along a chain. Further evidence that smaller changes lead to effective conformational changes was obtained from preliminary investigations of the cyclotetradecene system. The effects of torsional perturbations in the ring tended to be localized and did not affect the other parts of the ring. Finally, it was found that selective perturbation discovered the 10 best conformations of cyclohexadecane 2.5 times more rapidly than general kicking.

After each perturbation described above, Burkert and Allinger's MM2 program [14] was used to determine the strain energy. Because of the shallow gradients for these molecules the normal termination condition ( $\Delta E_{\text{strain}}/\text{iteration}$ ) for MM2 was made more than an order of magnitude more stringent. This drastically increased the time required to perform each minimization, but significantly reduced the number of structures which showed a dihedral angle difference of  $2^\circ$  to  $5^\circ$  for each dihedral angle, but which were found to be the same on exhaustive minimization. After minimization, duplicates and enantiomers were discarded and unique conformations were added to the library. This elimination procedure is based on the comparison of strain energies and torsion angles.

Since MMONTOR is a stochastic program, it is possible that some conformations could be missed. To get a feeling of the reliability of the program, MMONTOR was tested on medium and large rings which had been previously examined by Dale using his semi-quantitative approach [11] and later confirmed quantitatively by Saunders [18]. It reproduced all of the conformations of medium-sized rings ranging from cyclodecane to cyclohexadecane found by these researchers. MMONTOR also reproduced all of the low-energy conformations for cycloheptadecane reported by Saunders et al. [21]. These results are not explicitly reported in this paper, but are used in the section on the energy distributions for conformations of three ring sizes. MMONTOR was allowed to run more than three times longer (CPU time) for the cyclooctadecane, cyclononadecane and cycloicosane runs than was required to exhaustively reproduce the results for cycloheptadecane. Cyclounicosane and larger rings are currently under investigation. Partial results from these studies are used as supportive evidence below, but will be reported in full detail in a later paper.

All the MMONTOR calculations were carried out using a Convex C-210 computer. The program is about 2 to 3 times slower than others reported in the literature, largely due to the facts that it does not perform any preliminary screening on partially minimized structures, it retains the conformations above 3 kcal/mol of the lowest energy conformation and that it utilizes a simplistic duplicate searching technique. However, the program was not optimized since this analysis was only going to be performed on a limited number of molecules to obtain a library, instead of being used as a general method for generating many different large rings.

Once MMONTOR completed its run, the ten lowest energy conformations for each ring system were checked as local minima using MOPAC 6.0 using both PM3 and MNDO Hamiltonians and the keyword PRECISE. The MOPAC conformations were compared to the MM2 results utilizing the *compare* function of MacMimic [23]. All of the conformations were confirmed as being local minima, and were visually the same for both MM2 and MOPAC. Typical RMS difference values were less than 0.05 Å.

## RESULTS

The strain energies and dihedral angles for the 30 best conformations of cyclooctadecane,

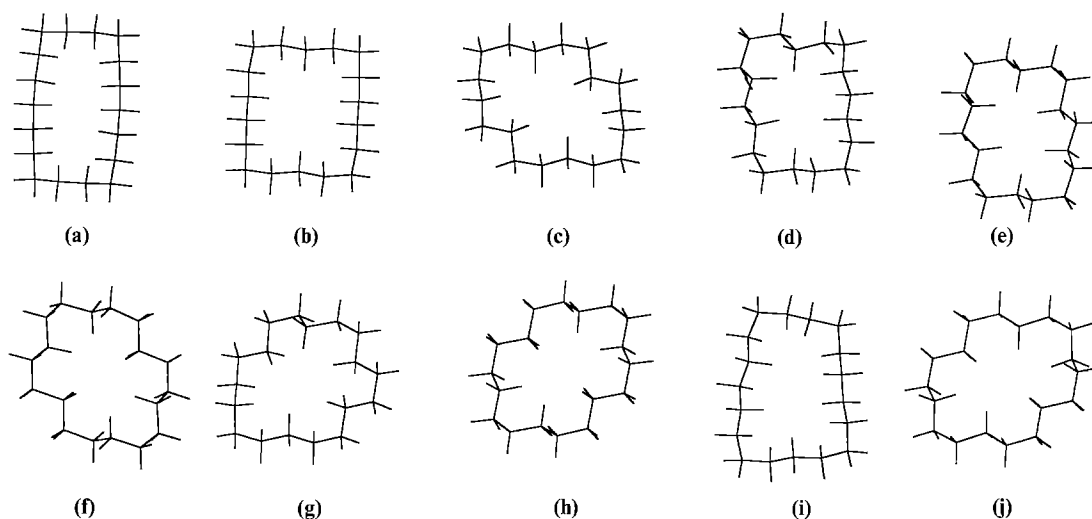


Fig. 1. Ten lowest energy conformations for cyclooctadecane.

cyclononadecane, and cycloicosane are shown in Tables 1, 2 and 3. The ten best conformations for each molecule are shown in Figs. 1, 2 and 3. The distribution of the number of conformations found within certain energy ranges compared to the most stable conformation found is shown in Table 4.

The distributions of individual dihedral angles and multiple dihedral angles may provide a useful insight into the conformational properties of these rings and help in devising an axiomatic system for the conformations of large flexible cyclic molecules. The triples and quadruples of these dihedral angles describe the shape of the side chains as well as the bends involved in various

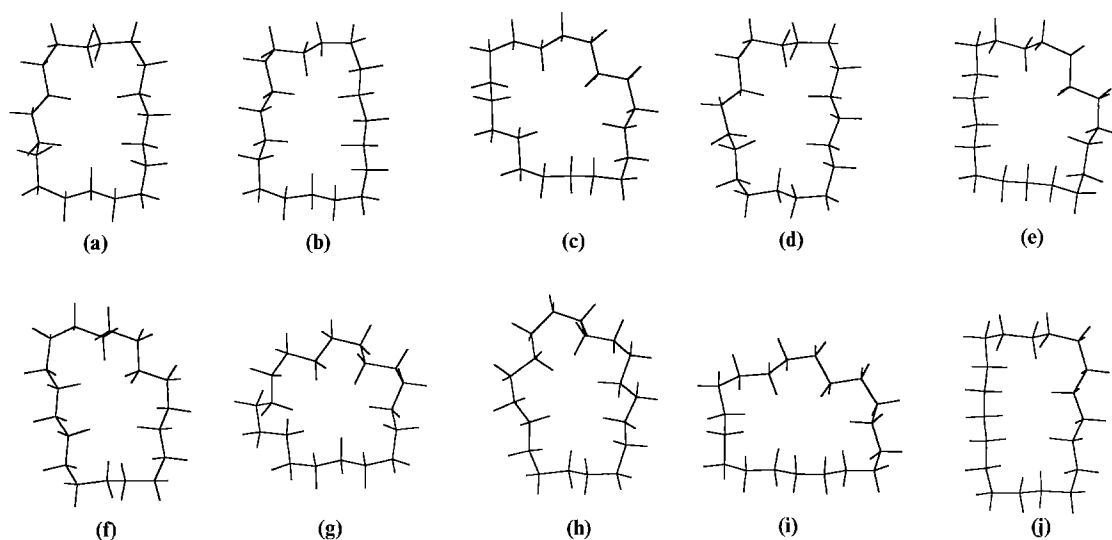


Fig. 2. Ten lowest energy conformations for cyclononadecane.



TABLE 2  
TORSION ANGLES FOR THE 30 LOWEST ENERGY CONFORMATIONS OF CYCLONONADECANE

(Strain energy	Torsion angles																		
19.6566	51.9	60.3	-169.2	178.6	-166.5	-178.6	-54.4	-52.9	-175.2	-172.3	64.3	54.4	167.3	62.3	170.1	173.1	56.7	58.0	172.1
19.7653	56.5	173.3	170.5	171.8	49.5	60.5	-171.6	-179.1	-53.1	-54.9	178.2	-172.0	175.6	-173.8	58.7	49.2	170.6	54.5	52.4
19.8749	75.7	175.7	-170.5	-67.3	175.9	175.5	52.9	58.3	179.7	66.7	175.6	173.4	74.0	-165.4	-173.3	-54.0	-54.3	-172.2	-168.9
19.9170	57.8	55.7	178.0	173.6	-174.6	173.4	-57.8	-50.2	-171.7	-57.6	-52.7	-165.3	-164.6	-52.9	-169.3	-172.0	67.6	60.7	174.1
19.9707	73.1	175.5	-174.4	-71.0	167.6	179.4	51.1	56.2	-175.0	177.4	176.4	59.2	66.5	-173.5	-168.3	-55.5	-56.7	-170.6	-171.6
19.9785	60.0	55.9	171.7	55.9	58.1	178.5	177.5	-178.2	176.4	-96.2	63.8	66.0	177.7	77.3	-178.7	-167.0	-61.8	-175.3	-179.8
20.0008	61.6	51.9	161.6	56.0	60.5	167.8	-179.9	-74.9	-175.2	170.1	54.5	64.5	-172.1	77.9	-176.3	-170.6	-60.3	-175.5	-179.7
20.0080	58.8	51.2	169.4	56.1	55.5	169.2	173.8	-76.0	-172.5	167.7	61.8	68.5	177.1	64.7	61.6	172.3	69.5	173.7	-176.7
20.0212	60.1	59.9	167.9	55.0	63.8	-173.4	-177.7	-165.7	-179.7	-51.4	-52.6	177.6	-160.6	75.1	176.2	-173.9	-69.8	-177.9	171.1
20.1239	-62.0	170.8	179.2	170.3	173.9	52.5	58.4	-178.6	171.4	-96.9	65.3	178.9	-174.9	-170.1	-171.6	-52.9	-61.3	-178.3	-57.6
20.1520	59.4	55.1	162.5	51.7	61.5	-178.4	-177.6	-56.8	-166.3	-166.4	-55.8	177.5	-171.9	56.6	51.6	173.6	62.2	169.7	170.8
20.2530	51.9	60.0	-170.9	178.1	-167.5	-178.6	-53.7	-55.8	-173.4	-59.5	-61.9	-65.6	-167.0	-75.5	175.8	166.0	56.3	60.3	170.8
20.3405	-58.1	-169.4	-52.9	-60.6	176.6	175.0	54.0	59.1	-178.0	-179.8	177.6	54.0	64.4	-160.4	-172.7	-52.6	-54.3	-172.1	-164.1
20.4149	59.1	174.0	167.7	69.5	-168.7	-174.8	-53.7	-53.6	-175.0	-167.2	69.2	167.2	175.1	58.3	173.1	57.6	50.8	57.9	175.1
20.4760	59.6	53.5	59.6	-179.9	-74.4	173.0	-61.0	-51.6	-172.5	-58.5	-52.0	-168.6	-163.3	-54.9	-175.5	-176.4	61.3	55.9	172.3
20.5222	174.0	-65.3	-67.1	171.9	174.5	171.8	-63.9	-53.8	-169.5	-59.8	-53.8	-165.6	-165.1	-55.2	-175.1	-171.0	60.3	49.2	173.7
20.5331	55.3	55.3	169.9	54.2	56.3	175.1	173.3	177.7	171.8	-99.2	61.8	68.2	179.2	73.1	176.6	179.7	62.9	166.7	58.5
20.6492	95.7	-65.6	-65.7	-176.8	172.2	-173.2	-69.8	-69.0	-172.0	-60.6	-57.1	-172.7	178.7	69.4	-179.3	-172.7	-61.9	-177.7	-174.8
20.6723	66.4	67.2	-172.6	179.8	-170.6	-176.2	-49.4	-58.8	169.5	179.9	55.8	52.9	173.4	170.7	176.3	178.6	-65.3	100.7	-175.0
20.6798	56.8	54.6	171.7	60.2	58.9	168.2	-178.3	-78.5	-176.7	165.7	62.3	66.6	176.5	96.2	-60.1	-176.4	-176.7	174.5	-179.6
20.6928	50.2	57.9	-174.9	174.9	-172.5	177.5	-54.9	-52.3	179.5	-168.8	60.9	162.0	171.9	52.5	173.2	169.8	-80.7	162.8	174.5
20.7564	174.0	177.9	-76.8	162.8	177.3	52.3	55.6	179.9	173.2	-178.9	167.9	-97.2	63.3	179.2	-170.7	-57.5	-177.5	-179.0	64.0
20.7829	-176.1	170.3	64.6	63.2	169.4	-172.8	-61.5	-63.3	-177.4	173.4	56.8	57.1	173.1	-179.4	-74.9	177.6	170.5	60.7	-97.1
20.7912	53.1	61.4	-177.3	178.3	-169.3	175.9	-52.1	-51.4	175.1	-160.3	66.9	165.9	174.8	56.2	165.3	57.4	57.4	57.2	166.1
20.7980	50.9	54.2	-175.4	167.7	-176.2	173.5	-59.1	-51.6	-173.3	-176.5	75.2	76.8	-177.0	75.5	176.2	-170.2	-71.1	167.6	179.4
20.8020	-82.8	-175.7	165.2	61.4	69.4	178.5	62.2	56.6	174.7	178.7	177.0	60.8	53.6	52.0	167.0	53.8	54.0	164.1	168.5
20.8197	54.8	54.0	175.2	165.8	-65.6	-162.9	-174.7	-53.3	-172.8	-179.5	59.3	65.4	-171.2	78.6	175.0	-167.6	-72.2	173.3	172.6
20.8481	75.5	175.9	-173.9	76.9	-161.4	178.8	-49.5	-56.5	170.3	177.8	58.1	169.2	167.0	56.6	61.3	169.1	56.7	66.1	-172.3
20.8628	59.5	50.4	162.9	55.3	56.3	163.5	166.7	52.1	168.1	53.9	52.0	62.4	-177.1	73.4	-177.7	-172.0	-63.8	180.0	180.0
20.8698	65.4	174.4	167.6	68.4	-168.6	-172.0	-55.9	-55.3	-167.2	-174.9	70.4	59.3	167.2	58.6	163.7	173.3	48.6	58.7	-174.4





conformations. This analysis can give a good correlation between stability and shape of the ring. Therefore, all the conformations within 3 kcal/mol of the lowest energy conformations were further analyzed. The exact numerical values of the dihedral angles were converted to the common symbolic terms eclipsed (*e*), gauche (*g*), staggered (*s*) and anti (*a*). The classification was performed by assigning symbolic values to angular sectors (e.g.  $+41^\circ$  to  $80^\circ$ ), and then examining which sector contained the given dihedral. The sectors surrounding the classical *g*<sup>+</sup>, *g*<sup>−</sup> and *a* angles were smaller ( $40^\circ$  inclusive) than the sectors between them ( $80^\circ$  inclusive) to emphasize distortions from the classical angles. The assignments are: dihedrals falling in the sector from  $-40^\circ$  to  $+40^\circ = e$ ,  $41^\circ$  to  $80^\circ = g$ ,  $81^\circ$  to  $160^\circ = s$ , and  $161^\circ$  to  $-161^\circ = a$ . Gauche and staggered bonds are given signs, *g*<sup>+</sup>, *g*<sup>−</sup>, *s*<sup>+</sup> and *s*<sup>−</sup> depending on the sign of the dihedral angle. Table 5 shows the triples and Table 6 shows quadruples of dihedral angles.

## DISCUSSION

### *Shape of the most stable conformations for large rings*

As early as 1930 it was thought that the lowest energy conformations of large rings would have rectangular shapes [24]. In 1940 Pitzer [5] suggested that these conformations would lie on the diamond lattice. The reasoning behind this was as follows: The most stable conformations of a butane-like chain are the staggered forms gauche<sup>+</sup> (*g*<sup>+</sup>), gauche<sup>−</sup> (*g*<sup>−</sup>) and anti (*a*). The anti form is the most stable of these. In any chain of methylene units the most favorable conformations will be those where the bonds adopt these staggered conformations. This is known as 'laying upon the diamond lattice'. Any deviation from this diamond lattice must be higher in energy than some diamond lattice form. The most stable conformation for any chain will be the one with all of the bonds in the anti conformation. This would hold true for large rings as well, except that a certain number of gauche bonds must be allowed to enable ring closure. In very large rings it is possible to affect this ring closure (while avoiding unfavorable *g*<sup>+</sup> *g*<sup>−</sup> pairs) with as few as 8 gauche bonds

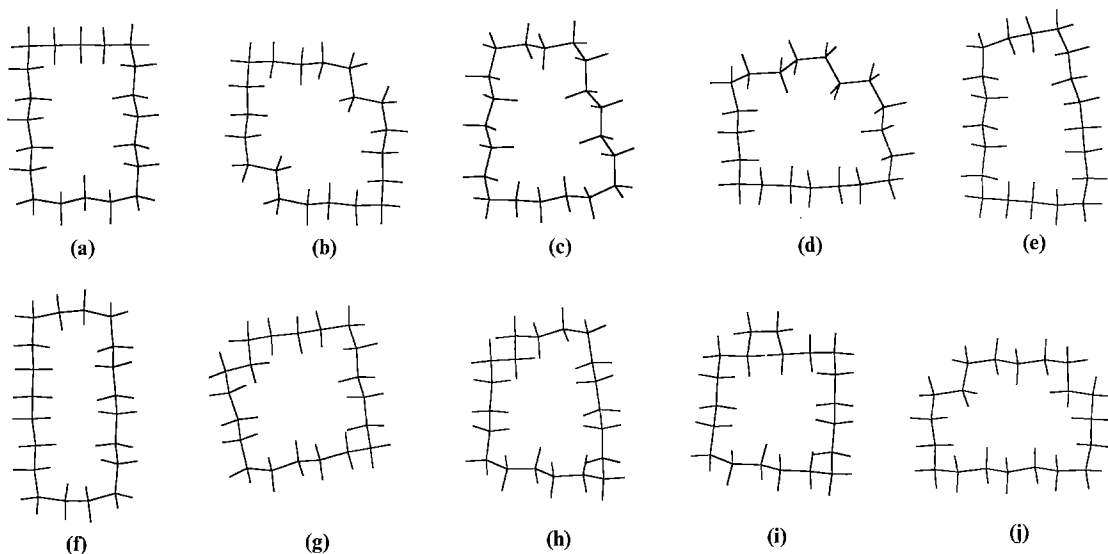


Fig. 3. Ten lowest energy conformations for cycloicosane.

TABLE 4  
NUMBER OF CONFORMATIONS GENERATED BY MMONTOR

Confs. within kcal	Cyclooctadecane		Cyclononadecane		Cycloicosane	
	lowest energy	18.21	lowest energy	19.657	lowest energy	18.512
	total confs.	1.922	total confs.	1.890	total confs.	1.566
	No. of confs.	% confs.	No. of confs.	% confs.	No. of confs.	% confs.
1	13	0.7	18	1.0	1	0.1
2	24	1.2	67	3.5	14	0.9
3	59	3.1	169	8.9	48	3.1
4	154	8.0	215	11.4	89	5.7
5	214	11.1	257	13.6	155	9.9
6	307	16.0	279	14.8	201	12.8
7	302	15.7	261	13.8	193	12.3
8	276	14.4	208	11.0	211	13.5
9	208	10.8	158	8.4	184	11.7
10	142	7.4	108	5.7	175	11.2
11	95	4.9	63	3.3	104	6.6
12	51	2.7	42	2.2	74	4.7
13	17	0.9	19	1.0	53	3.4
14	11	0.6	7	0.4	24	1.5
15	7	0.4	7	0.4	13	0.8
16	2	0.1	2	0.1	3	0.2
17	0	0.0	0	0.0	2	0.1
18	0	0.0	1	0.1	1	0.1
19	0	0.0	1	0.1	0	0.0
20	0	0.0	0	0.0	0	0.0
> 20	40	2.1	8	0.4	21	1.3

(arranged as  $g+g+$  or  $g-g-$  pairs). Turns made up of  $g+g+$  ( $g-g-$ ) pairs give a  $90^\circ$  bend in space; thus four pairs give a total included angle of  $360^\circ$  which describes a quadrilateral enclosure. More acute bends lead to unfavorable transannular H-H interactions [25] while less acute bends would require a greater number of  $g+g+$  or  $g-g-$  pairs.

Given these four corners, the most stable form will be the one in which the rest of the bonds adopt anti conformations. This will be geometrically possible if the ring has an even number of atoms,  $N$ , where  $N \geq 14$ . Of course, not all combinations of  $g+g+$  (or  $g-g-$ ) pairs and anti chains can give stable rings. If the anti chains are not parallel and of equal length (i.e. describe a rectangle), then the gauche turns or the anti chains will have to bend to accommodate the geometrical irregularities. This bending will also be required in odd-membered rings, where the sides cannot be equal in length. A short proof of this is as follows: assume we have a ring with an odd number of bonds,  $N$ . If we use 8 bonds in the gauche turns, this leaves us with  $M = N - 8$  bonds, which is also odd. We cannot divide an odd integer  $M$  into four integer segments of equal length. Therefore, odd-membered rings cannot adopt a simple low-energy rectangular conformation. As we will show, this early assumption turns out to be a good heuristic, but misses some low-energy conformations which lie *near* the diamond lattice.

TABLE 5  
DISTRIBUTION OF DIHEDRAL ANGLE TRIPLETS

	Cyclooctadecane			Cyclononadecane			Cycloicosane		
	1 kcal	2 kcal	3 kcal	1 kcal	2 kcal	3 kcal	1 kcal	2 kcal	3 kcal
<i>g+ g+ a</i>	30	82	166	74	239	529	4	52	156
<i>g- g- a</i>	43	71	127	43	117	275	4	34	119
<i>g+ a a</i>	36	71	182	64	252	524	4	58	197
<i>g- a a</i>	40	71	150	56	191	434	4	48	148
<i>a a a</i>	12	19	36	23	69	187	4	41	107
<i>a g- a</i>	14	18	47	16	60	152	0	13	38
<i>a g+ a</i>	18	21	72	17	71	131	0	11	62
<i>g+ a g+</i>	15	25	61	22	65	143	0	7	36
<i>g- a g-</i>	16	18	42	9	26	89	0	5	19
<i>a a s-</i>	0	2	12	3	26	76	0	0	9
<i>a a s+</i>	0	2	14	1	9	62	0	0	2
<i>g+ s- a</i>	0	0	11	3	20	70	0	0	5
<i>g- s+ a</i>	0	0	21	1	16	65	0	0	3
<i>a g+ s-</i>	0	1	8	1	13	64	0	0	1
<i>a g- s+</i>	1	3	26	0	16	55	0	0	3
<i>g+ g+ g+</i>	5	8	18	4	13	36	0	2	13
<i>g- g- g-</i>	2	3	6	1	5	19	0	1	12
<i>g+ g+ s-</i>	0	2	7	2	10	34	0	4	4
<i>g- g- s+</i>	1	1	4	1	1	23	0	0	2
<i>g+ a s+</i>	0	1	8	0	9	33	0	0	1
<i>g- a s-</i>	0	0	8	0	7	20	0	0	0
<i>g+ a g-</i>	0	4	7	1	4	20	0	2	12
<i>g+ g+ s+</i>	0	0	0	0	5	19	0	0	1
<i>g- g- s-</i>	0	0	0	0	6	2	0	0	0
<i>a g- s-</i>	0	1	2	0	1	16	0	0	0
<i>a g+ s+</i>	0	1	1	0	1	10	0	0	1
<i>a s+ a</i>	0	1	4	0	1	10	0	0	0
<i>a s- a</i>	0	1	4	0	6	8	0	0	2
<i>g+ s+ g+</i>	0	0	0	0	2	9	0	0	0
<i>g- s- g-</i>	0	0	0	0	3	1	0	0	0
<i>g+ s+ a</i>	0	1	1	0	1	9	0	0	1
<i>g- s- a</i>	0	0	0	0	0	7	0	0	0
<i>g+ s- g-</i>	0	1	2	0	1	9	0	0	0
<i>g+ s- g+</i>	0	1	1	0	2	8	0	2	0
<i>g- s+ g-</i>	1	2	5	0	0	4	0	0	0
<i>a s- s+</i>	0	0	1	0	0	7	0	0	1
<i>a s+ s-</i>	0	0	0	0	0	5	0	0	0
<i>g+ s+ g-</i>	0	0	0	0	1	6	0	0	1
<i>g- s+ s-</i>	0	0	1	0	0	4	0	0	1
<i>g+ s- s+</i>	0	0	0	0	0	3	0	0	0
<i>s- a s-</i>	0	0	0	0	0	4	0	0	0
<i>s+ a s+</i>	0	0	4	0	0	3	0	0	0

*Shape of the most stable conformations for cyclooctadecane*The lowest energy conformation of cyclooctadecane **1a** (as determined by the MM2 force field)

TABLE 6  
DISTRIBUTION OF DIHEDRAL QUADRUPLS

Cyclooctadecane			Cyclononadecane			Cycloicosane		
1 kcal	2 kcal	3 kcal	1 kcal	2 kcal	3 kcal	1 kcal	2 kcal	3 kcal
aa g+ g+	13	44	81	39	141	283	40	108
aa g- g-	21	45	62	28	80	153	4	85
g- aa g+	20	40	98	34	128	239	1	86
aa g- aa	18	23	64	28	95	222	0	60
aa g+ aa	23	26	94	24	98	174	0	87
aa g- a	18	23	64	28	95	222	0	60
aa g+ a	23	26	94	24	98	174	0	87
g+ g+ aa g+	17	34	79	34	88	203	0	44
g- g- aa g-	22	25	57	15	31	104	0	25
aa g+ g+ a	10	32	62	32	101	203	2	62
aa g- g- a	19	32	55	20	50	105	2	46
aa aa g+	6	15	26	15	52	122	2	71
aa aa g-	10	17	16	11	28	85	2	45
aa g+ aa g+	13	15	41	10	41	77	0	28
aa g- aa g-	10	10	23	3	20	59	0	13
aa g+ g+ g+	10	16	35	8	25	71	0	26
aa g- g- g-	4	6	12	2	10	38	0	24
aa aa aa	4	3	10	9	24	63	2	46
s- g+ aa	0	1	7	0	13	60	0	1
s+ aa g-	1	3	23	0	16	50	0	3
g+ aa g+	5	7	24	7	26	55	0	18
g- aa g-	5	6	15	5	15	37	0	8
aa s- g+	0	0	10	1	8	47	0	5
s- aa g+	0	2	8	1	17	53	0	2
s+ aa g-	0	2	6	1	8	34	0	3
aa g+ s-	0	0	7	1	10	46	0	1
aa g- s+	0	0	17	0	15	41	0	2
aa s+ aa	0	0	7	1	10	46	0	1
aa s- aa	0	0	17	0	15	41	0	2
aa g- g-	0	2	6	2	10	32	0	4
s- g+ g+	0	2	4	2	10	32	0	4
s+ g- g-	0	0	4	1	1	23	0	2
s- g+ g-	0	0	2	0	1	26	0	1
s+ g- g+	0	0	2	0	1	26	0	1
s- aa s-	0	0	5	0	5	15	0	0
aa s- g+	0	0	4	0	4	32	0	4
s- g+ g-	1	1	4	1	1	23	0	2
s+ g- g-	0	1	2	0	1	26	0	1
s- aa s-	0	0	2	0	2	15	0	0
aa s- g-	0	0	4	0	4	32	0	4
s- g- g+	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g+	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g+	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
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s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0
s+ g- g-	0	0	2	0	2	15	0	0
s- g- g-	0	0	2	0	2	15	0	0
s+ g+ g-	0	0	2	0	2	15	0	0
s- g+ g-	0	0	2	0	2	15	0	0

TABLE 6 (continued)

	Cyclooctadecane			Cyclononadecane			Cycloicosane		
	1 kcal	2 kcal	3 kcal	1 kcal	2 kcal	3 kcal	1 kcal	2 kcal	3 kcal
<i>g</i> <sup>-</sup> <i>a</i> <i>g</i> <sup>+</sup> <i>g</i> <sup>+</sup>	0	3	4	1	3	16	0	1	3
<i>g</i> <sup>-</sup> <i>a</i> <i>s</i> <sup>-</sup> <i>g</i> <sup>+</sup>	0	0	5	0	3	14	0	0	0
<i>g</i> <sup>+</sup> <i>a</i> <i>s</i> <sup>+</sup> <i>g</i> <sup>+</sup>	0	1	0	0	0	5	0	0	0
<i>g</i> <sup>-</sup> <i>a</i> <i>s</i> <sup>-</sup> <i>g</i> <sup>-</sup>	0	0	0	0	0	3	0	0	0
<i>a</i> <i>a</i> <i>s</i> <sup>-</sup> <i>a</i>	0	2	5	0	8	13	0	0	3
<i>a</i> <i>a</i> <i>s</i> <sup>+</sup> <i>a</i>	0	2	4	0	1	10	0	0	0
<i>a</i> <i>s</i> <sup>-</sup> <i>a</i> <i>a</i>	0	2	5	0	8	13	0	0	3
<i>a</i> <i>s</i> <sup>+</sup> <i>a</i> <i>a</i>	0	2	4	0	1	10	0	0	0
<i>a</i> <i>g</i> <sup>+</sup> <i>s</i> <sup>-</sup> <i>g</i> <sup>+</sup>	0	1	1	0	2	11	0	0	0
<i>a</i> <i>g</i> <sup>-</sup> <i>s</i> <sup>+</sup> <i>g</i> <sup>-</sup>	1	3	9	0	0	7	0	0	0

has a rectangular shape (see Fig. 1). This shape is described in Dale's [11] nomenclature as [6363] (i.e. a rectangle of 4 sides of length 6, 3, 6 and 3, respectively). Figure 1 shows the second best conformation (**1b**) as being the [5454] conformation. MM2 calculates that this conformation is 0.282 kcal/mol higher in energy than the lowest energy conformation. It has been suggested that the increased stability of the [6363] conformation arises from van der Waals attractive forces between the hydrogen atoms on the opposite side of the long chains, whereas the greater distance between the parallel chains in the [5454] conformer decreases the van der Waals stabilization. In fact, our preliminary studies show that for larger cycloalkanes ( $C_{28}$  or more) the attractive van der Waals forces can actually cause the ring to be squashed inwards (as shown in Fig. 4 for  $C_{30}$ ).

The third most stable conformation (**1c**) is the first member of a new class of large rings. Dale's analysis assumed that all large rings would be essentially very large 3-, 4-, or 5-sided rings, where the sides would be slightly deformed all anti-chains. Exhaustive studies performed before this date have focused on rings which are smaller than cyclooctadecane. This sort of shape can be shown to be impossible (without transannular strain) in rings of less than 18 members. In this new class of rings a simple gauche (*ag*+*g*+*a* or *ag*-*g*-*a*) turn is replaced by a 'nick', which is described as *g*+*aag*+ or *g*-*aag*-. It can be seen that the total number of gauche bonds in the ring does not increase, so we would expect the energy of these conformations to be similar to that of the most stable conformation. MM2 calculates that this conformation will be only 0.6405 kcal/mol less stable than the most stable [6363] conformation. These 'nicked' conformations become increasingly more important as the ring size increases. We have augmented Dale's nomenclature to represent this conformation as [4n34n3], where n represents a nick comprising two bonds.

Diamond lattice (DL) structures account for the three lowest energy cyclooctadecane conformations. The next DL conformation, shown in Fig. 5, has a strain energy which is more than 3.6 kcal/mol higher in energy than the most stable conformation. This conformation corresponds to an 18-crown-6 conformation, and is destabilized by the transannular H-H interactions. This conformation corresponds to the first tetra-nick compound. While we have been able to generate comparatively stable tetra-nick compounds in larger rings, 18-membered rings are too small to accommodate the demands of this structure easily.

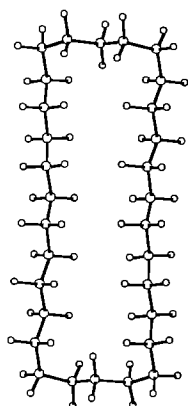
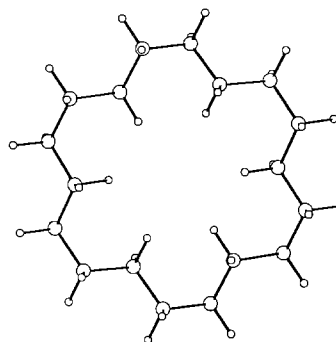
Fig. 4. The rectangular conformation for  $C_{30}$ .

Fig. 5. The crown conformation for cyclooctadecane.

The remaining conformations in Fig. 1 can be seen to be non diamond lattice rings. As the rings deviate more from the most stable rectangular or nicked forms ([6363], [5454] or [4n34n3]) the energy rises as the amount of distortion increases. The fourth conformation (**1d**) is a [6363] to [6453] deviation. Since the sides are of unequal lengths, the rectangle must be skewed and the bonds cannot lie exactly on the DL. However, the amount of distortion is small, as can be seen by examining Table 1. The individual dihedral angle in conformation **1a** differs from 'pure' DL angles by as much as  $4.2^\circ$  (in the gauche bonds) and  $6.5^\circ$  (in the anti bonds). In **1d** the difference rises to  $9.2^\circ$  (gauche) and  $12.9^\circ$  (anti). In general we have found that the anti bonds show a greater tendency to deform. This was first observed in MM2 calculations and has been confirmed with MOPAC/MNDO and MOPAC/PM3. Because of the relatively small amounts of distortion necessary, conformation **1d** is only 0.65 kcal less stable than the best conformation.

#### *Most stable conformations of cyclononadecane*

Odd-membered rings cannot lie along the diamond lattice. It is easiest to imagine their structures as arising with attempts to come as close to an even-membered DL structure as is possible. The most stable 18-membered ring structures are [6363] and [5454], while we will see that the best 20-membered ring structures are [6464] and [4n44n4]. Thus we find that the two most stable cyclononadecane conformations (**2a**, **2b**) are two variations [6364], which can be viewed as mixtures of the stable 18-membered [6363] conformation and the stable 20-membered [6464] conformation. The next most stable conformation (**2c**) [4n34n4] can be viewed as a mixture of cyclooctadecane [4n34n3] and cycloicosane [4n44n4]. This trend continues with other conformations such as [454n4] (**2e**) which can be seen as a hybrid of cyclooctadecane [4545] with cycloicosane [4n44n4].

The calculated strain energies of the cyclononadecane conformations are in general higher than that of the cyclooctadecane conformations. The first ten cyclooctadecane conformations range in energy from 18.21 to 19.05 kcal/mol, while the first ten cyclononadecane conformations range in energy from 19.65 to 20.12 kcal/mol. This is an effect of not being able to lie along the diamond lattice and is not an effect of increased molecular weight, as can be seen by the fact that the most stable cycloicosane conformation is calculated to have a strain energy of 18.51 kcal/mol.

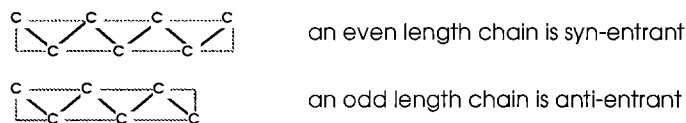


Fig. 6. Definitions of syn and anti entrant ribbons.

### *Most stable conformations of cycloicosane*

While cyclooctadecane showed less than 0.03 kcal/mol energy difference between the [6363] and [5454] conformations, cycloicosane shows almost 1.4 kcal/mol difference between the best (**3a**) [7373] and next best (**3b**) [6464] conformations. Although the van der Waals attraction across the 'narrower' [7373] conformation might be expected to render it more stable than the less compact [6464] ring (MM2 calculations do show that the transannular VDW attraction of the [7373] is better by 0.86 kcal/mol), this effect is more than overcome by the torsional strain necessary to close the [7373] conformation.

This follows naturally from the geometrical requirements of large rings made up of sides consisting of a series of nearly perfect anti bonds, connected at the corners by gauche turns or nicks. The sides can be considered as ribbons, with the methylenes alternating on the top and bottom sides (see Fig. 6). In a side with an odd number of bonds, the 'shared' methylenes on the ends of the ribbon are on opposite sides of the ribbon. We term this arrangement anti entrant. On a side with an even number of bonds the 'shared' methylenes on the ends are on the same side of the ribbon (syn entrant). Certain arrangements of syn entrant and anti entrant sides can lie along the DL. This is shown in Fig. 7, where [6464] cycloicosane and [5454] cyclooctadecane both form DL rings. However, Fig. 8 shows that a series of four anti entrant sides does not form a closed ring on the DL – instead they form a portion of a helical structure. If the sides of the [5555] conformer are aligned on the DL, then the ends miss by 5.4 Å. Closure of such an [odd-odd-odd-odd] ring requires substantial twisting of the bonds. This is the case with [7373] and [5555] cycloicosane. This observation is consistent with the fact that both Allinger et al. [26] and Shanon et al. [27] have calculated that the [odd-odd-odd-odd] conformation of [3535] cyclohexadecane is substantially higher (3.4 kcal/mol) in energy than the [4444] conformation.

The length of the sides of such distorted rings seems to be critical in determining the stability of the resulting distorted structures. Since the strain of twisting a torsion angle is not a linear function of the angle, twisting a larger number of bonds by a small amount can be very favorable compared to twisting a smaller number of bonds by a large amount. Short sides (3 through 5) contain too few bonds to distribute the angular deviation without a substantial energy penalty. Thus the [3535] conformation of cyclohexadecane and the [5555] conformation of cycloicosane are both highly strained (more than 3 kcal above the most stable conformation). On the other hand the seven-bond side [7373] cycloicosane ring is also enough to distribute the distortion with 'only' 1.4 kcal/mol of strain.

### *Comparison of the energy distributions in the three ring sizes*

Cyclooctadecane has several nearly equal energy conformations: [6363], [5454] and [4n34n3]. Cyclononadecane has an even larger of number of nearly equa-energetic conformations. This can be ascribed to the fact that none of the conformations can lie on the DL, which means that they



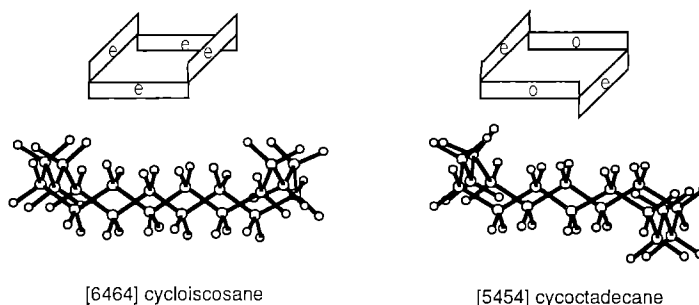


Fig. 7. Analysis of [6464] cycloicosane and [5454] cyclooctadecane rings in 'ribbon' forms.

contain some strain, and twist so as to lie near the DL and minimize the strain. On the other hand the [6464] conformation of cycloicosane is more than 1 kcal/mol more stable than the next best conformation. This is due to the fact that alternate rectangular or nicked conformations are inherently poor; a [7373] conformation is possible, but must be twisted away from the DL. A [5555] conformation is even worse. Nicked conformations can be thought of as mutations of rectangular rings. The second best cycloicosane conformation is a [4n44n4], which can be thought of as a mutation of [5555]. Apparently, nicks can relieve some of the problems in an [odd-odd-odd-odd] ring, but not all of them. We are currently studying the effects of nicks, double nicks, and other mutations, and will report on that in a future paper. Thus the cyclooctadecane ring has a number of equally-good conformations, the cyclononadecane ring has a number of equally-poor conformations, but the cycloicosane ring has a single good conformation and a number of poor conformations.

By examination of Table 4 it can be seen that in the case of cyclooctadecane there were 13 conformers (0.7% of all the conformers) within 1 kcal of the lowest energy conformer. In the case of cyclononadecane there were 18 conformers within 1 kcal (1.0%). However, in the case of cycloicosane there was only 1 conformer (0.1%) within 1 kcal/mol of the lowest energy conformer. A graph of the number of conformations within each energy range (within 1 kcal of the best, etc.) for ring of size 16 through 20 is shown in Fig. 9. It can be seen that in the first 1.0 kcal/mol range there are two groups; the three intermediate-sized rings, cycloheptadecane through cyclononadecane, show a cluster of several conformations amounting to  $\sim 1\%$  of the total found, while cyclohexadecane and cycloicosane only had one conformation each in this range. Preliminary results for cyclounicosane rings also demonstrate a cluster of about 1% of the conformations in this range. All of this is in agreement with the hypotheses put forward above that the cycloicosane

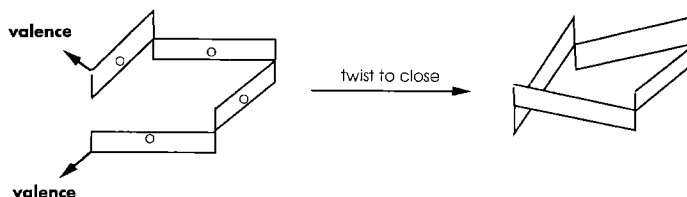


Fig. 8. Odd-odd-odd-odd ribbons form portions of helices, and cannot close without substantial twisting.

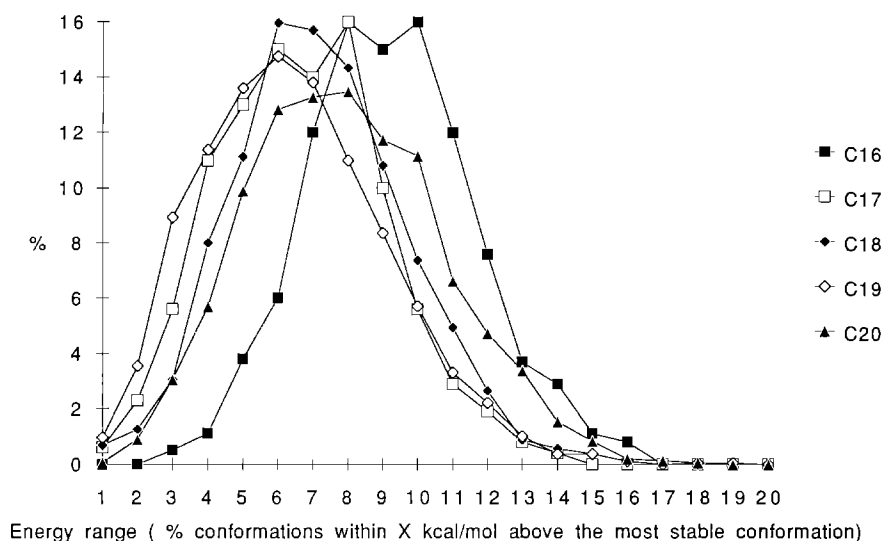


Fig. 9. Percentages of conformations for cyclohexadecane through cycloicosane rings within energy ranges of the most stable conformation.

and cyclohexadecane rings should show one conformation of exceptional stability, while cyclooctadecane should show several conformations of normal stability, and the non-diamond lattice rings should show a larger number of slightly strained conformations. This can be seen graphically in Fig. 10 where the more stable conformations of cyclohexadecane, cyclooctadecane and cycloicosane have been removed, shifting these curves to the left. The agreement of the shapes of the remaining curves is striking. This suggests that the mechanisms for strain relief in the *strained*

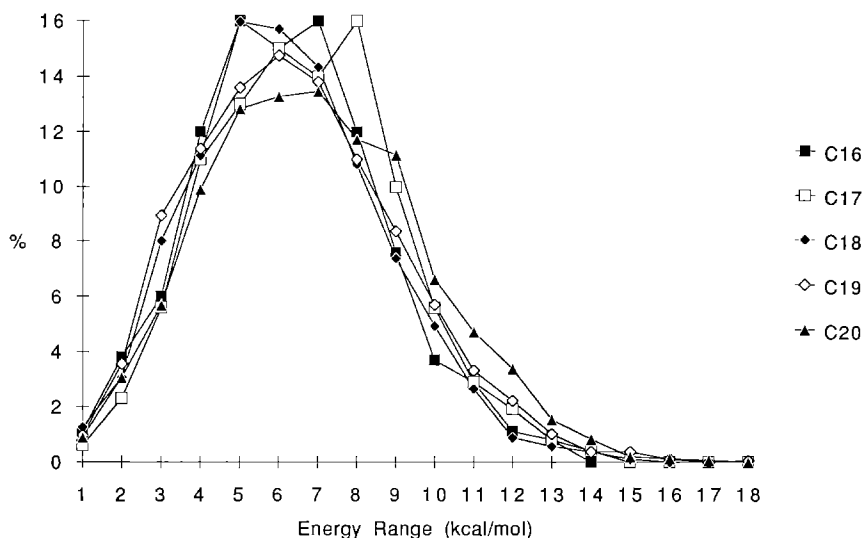


Fig. 10. Percentages of conformations for cyclohexadecane through cycloicosane rings within energy ranges of the most stable conformation, after removing those conformations which are of exceptional stability.

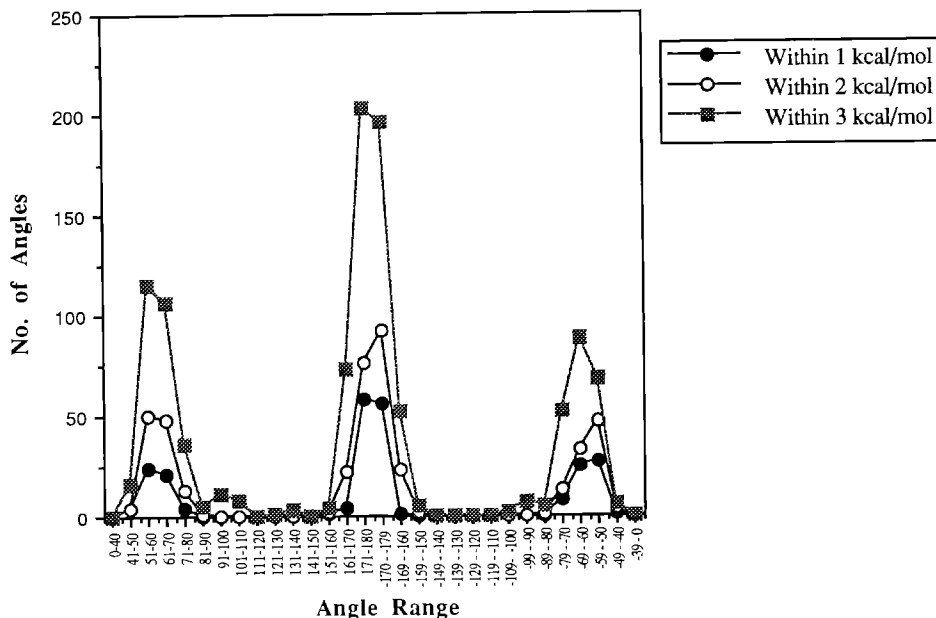


Fig. 11. Angle distribution in cyclooctadecane.

conformations seems to be independent of ring size or ability to fit on the diamond lattice. These factors only seem to be important for the most stable conformations, and become less important as the amount of strain increases past a certain point (about 1–2 kcal/mol). It is also interesting to note that there seems to be an upper limit to the amount of strain available in any ring before it relaxes to a less strained ring, and on average this seems to be about twice the transitional energy barrier for a *g* to *a* conversion (or vice versa). This observation was foreshadowed by Dale's paper of conformational interconversion, where he suggested that the most efficient process for strain relief consisted of the migration of one or two *gauche* bonds in a ring [12].

#### *Analysis of torsion angle distributions*

Figures 11 through 13 show the distribution of torsion angles in all the conformations within 3 kcal/mol of the lowest energy conformation in cyclooctadecane, cyclononadecane and cycloicosane, respectively. As expected, within the first 3 kcal/mol of the lowest energy conformer, most of the angles are very close to ideal *gauche* and ideal *anti* torsion angles. In cycloicosane, for example, in 63 low-energy conformations, we found only 14 angles that were in the  $-80^{\circ}$  to  $-159^{\circ}$  and  $81^{\circ}$ – $160^{\circ}$  ranges. Comparison of the shapes of the individual curves confirmed the expected results: as the strain energy increases the standard deviation of the each *gauche* or *anti* curve increases. As the strain increases, the ratio of *gauche* and nearly *gauche* bonds to *anti* bonds also increases. And finally, the standard deviations of the angles for cyclononadecane are greater than the SD for the DL rings.

Analysis of the appearance of the first staggered bonds within the three ring sizes agrees with the previous conclusion that cyclooctadecane and cycloicosane are stable ring sizes, while cyclononadecane contains inherent strain. The first staggered bond appears at 0.74 kcal/mol and

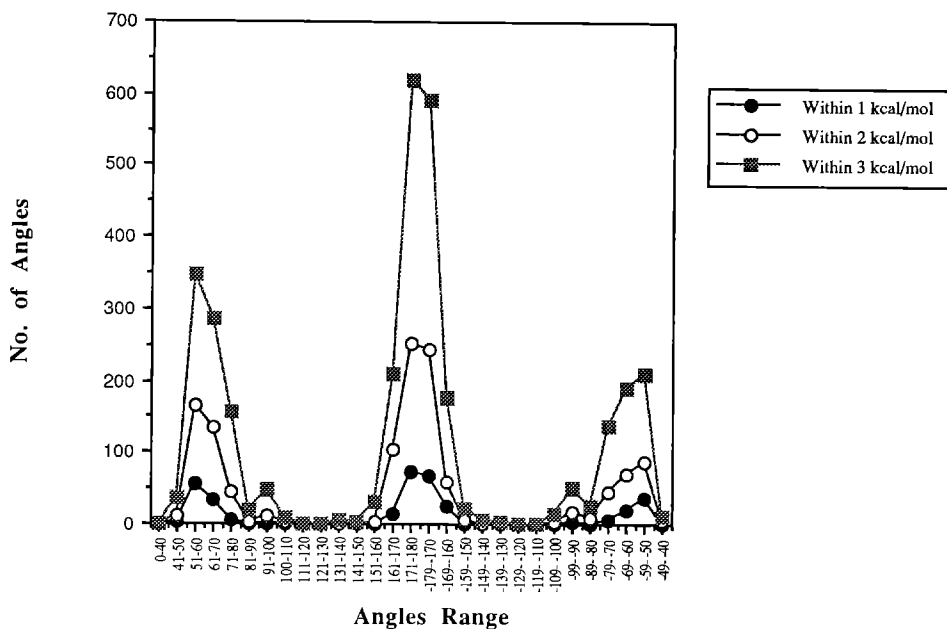
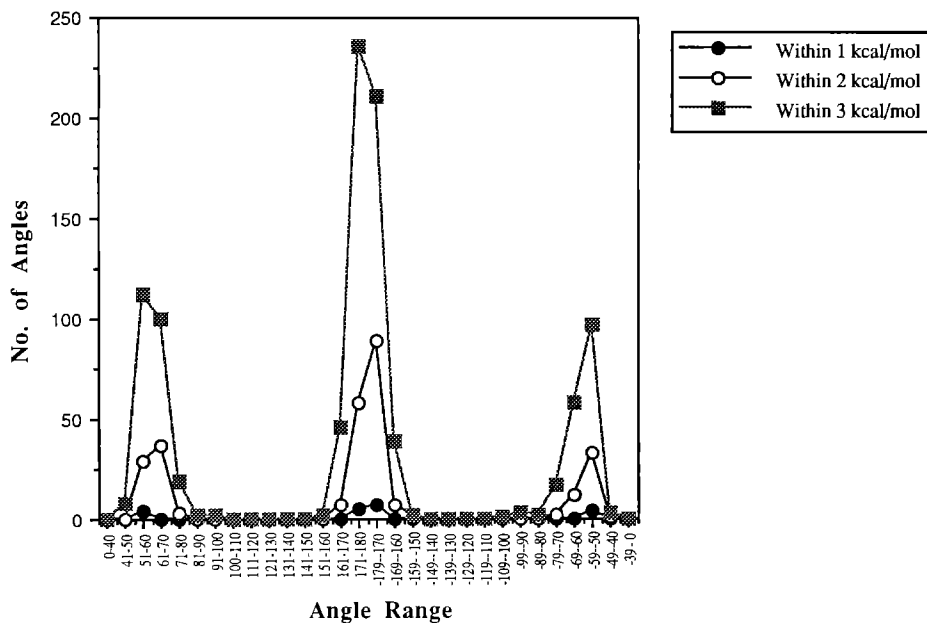


Fig. 12. Angle distribution in cyclononadecane.

1.39 kcal/mol above the energy of the most stable conformation for cyclooctadecane and cycloicosane, respectively, but it appears at only 0.32 kcal/mol above the best conformation in the case of cyclononadecane. No eclipsing bonds appear within 3 kcal/mol of the most stable confor-



mation in any of these rings. Analysis of the number of conformations within 3 kcal/mol of the most stable conformation which contain staggered bonds also confirms the conclusions about ring stability. There are 96 cyclooctadecane conformations within that energy range, of which 49 contain staggered bonds (51%), 254 cyclononadecane conformations with 206 containing staggered bonds (81%), but only 63 cycloicosane conformations with only 13 containing staggered bonds (21%). However, if the most stable cycloicosane conformation is eliminated as being 'extraordinary', and the range is examined for the 3 kcal above the second best conformation, 81 conformations contain staggered bonds out of 151 total rings (54%).

#### *Analysis of the distributions of torsion angle triples and quadruples*

The table of torsion angle triplets (Table 5) shows that 4 combinations of gauche and anti bonds ( $g+g+a$ ,  $g-g-a$ ,  $g+aa$ ,  $g-aa$ ) occur most frequently. The numbers for various enantiomeric triplets (e.g.  $g+g+a$  and  $g-g-a$ ) are not the same since MMONTOR discovered and eliminated enantiomeric conformations. The predominance of these triples is expected because  $g-g-$  and  $g+g+$  combinations represent a *corner* of the ring. The  $aag \pm$  combination can also be part of a  $g \pm aag \pm$  nick (where the signs are all consistent). The  $ag \pm a$  combination can be part of a nick, or in a bend in the side of a long ring, and is quite common. Other common triples include the  $g+ag+$  combination, which describes the length of the three sides of a  $[-3-]$  conformation, and the  $aaa$  combination.

Triples containing a staggered bond are less common, even in the strained odd-membered cyclononadecane ring. The combinations which show up at the lowest energies include representatives of a 'bent corner'  $g+s-$  or  $g-s+$ . Thus  $ag-s+$ ,  $ag+s-$ ,  $g+s-a$ , and  $g-s+a$  are all found within 1 or 2 kcal of cyclooctadecane and cyclononadecane, but only occur at strains above 2 kcal for cycloicosane.

The analysis of the quadruples shown in Table 6 reveal the same trend. Quadruples which correspond to corners ( $aag \pm g \pm$ ,  $aaag \pm$  and  $ag \pm g \pm a$ ) are common, as are those corresponding to sides of length 4 ( $g+aag-$ ,  $g-aag+$ ), sides of length 5 or greater ( $aaag \pm$ ), extended sides ( $aaaa$ ), and nicks ( $g+aag+$ ,  $g-aag-$ ,  $aag+a$ ,  $aag-a$ , etc.).

## CONCLUSIONS

The low-energy conformations for cyclooctadecane, cyclononadecane, and cycloicosane were discovered by MMONTOR, and the 30 best conformations for each ring size are presented in this paper. The most stable conformers follow Dale's general scheme, but several new shapes have been discovered. The most common are called 'nicked' conformations, and are increasingly important in the larger rings. Nicked conformations have been observed in modified large rings; 18-crown-6 exists as a tetra-nicked ring.

The ability of the ring to lie on the diamond lattice affects the distribution of the conformations with regard to energy, and the appearance of staggered bonds in the ring. The two rings which can lie on the diamond lattice (cyclooctadecane and cycloicosane) both demonstrated a relatively small number of conformations within 3.0 kcal/mol (96 and 63, respectively) with a smaller overall strain (18.2099 and 18.5122 kcal/mol, respectively) while cyclononadecane showed a relatively greater number of conformations starting at a relatively higher energy (254 conforma-

tions, 19.6566 kcal/mol). This trend is in agreement with previously published results [21] for cycloheptadecane (262 conformations, 19.06 kcal/mol).

Finally, the geometric requirements of these large rings seem to indicate that some rings will naturally adopt one or more comparably stable conformations (e.g. cyclooctadecane), while others will have a smaller number of conformations that are very stable (e.g. cycloicosane). Studies to see if this is a general phenomenon are currently underway and will be published at a later date.

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