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How Many Conformers Are There for Small *n*-Alkanes? Consequences of Asymmetric Deformation in GG' Segment

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Abstract: *Conformers have been generated exhaustively or nearly so for n-heptane, n-octane, n-nonane and n-decane using a new conformational space search program in combination with MM2 as the minimizer. When the duplications due to symmetry are ignored, they number 109, 347, 1101 and 3263, respectively These numbers are greater than* 3^n *(n is the number of internal C-C bonds), mainly due to the fact that a GG' sequence in the backbone chain deforms asymmetrically and approximately doubles the number of high-energy conformers. Based on these results, the aspects of conformer distribution in linear molecules are discussed. The proportion of high-energy conformers to the total number is predicted to increase rapidly with the increase in the chain length, whereas low-energy conformers having no GG' sequence increases only by* 2.4^n

To obtain reliable and accurate informations on the conformers and their distribution is a necessary condition for the study of flexible molecules, to which belong a great number of organic, organometallic, polymers, and bioactive compounds.[1] Yet, experimental means to study the multi-conformer mixture are limited, hence it is not surprising to realize that, to our knowledge, neither the total number nor the order of stabilities of the C-C rotamers for such a small molecule like *n*-octane has ever been described in chemical literature.[2] We present in this paper the first systematic and nearly exhaustive generation of all conformers for *n*-alkanes up to *n*-decane by means of a new conformer search program using MM2 as the minimizer. Results are analyzed in some detail in order to obtain perspectives on the problem of explosive increase in the number of conformations with the length of chain molecules.

COMPUTATIONAL METHODS

Instead of the old tree algorithm, which produces 3^n conformations at once from an input structure (n is the number of rotatable bonds),[3,4] a new conformation search algorithm for searching low-energy conformers has been developed.[5] Trial structures are produced by giving small local perturbations, in this case successive rotations at every internal bond by ±120° on the initial structure. Each trial structure contains only one more gauche bond and hence is ca 0.8 kcal/mol higher in energy than the initial structure. Take for example the global minimum AA (anti-anti) conformer of *n*-pentane. Successive stepwise rotation produces GA, G'A, AG and AG'; all are new (ignoring redundancy due to symmetry for the moment), hence they are saved. The AA conformer is now labeled as 'perturbed'. One of the saved conformers, *e.g.* GA, is next subjected to perturbation, producing G'A, AA, GG and GG'. The last two are new (saved), but the former two had already been saved, hence rejected after comparison with all the stored structures. Actually GG' consists of a pair of local minima, which will be mentioned below in more detail.

Our perturbation strategy produces a lot of duplicated structures, but for this reason does not miss any local minimum near the initial structure. Exhaustiveness of search is guaranteed by subjecting all of the saved (unique) conformers to the perturbation. This seemingly wasteful algorithm has been improved by pruning duplications at early stages of geometry-optimization through frequent comparison of dihedral angle arrays.[5,6,7] One of the notable features of the algorithm is a device by which the conformation search can be directed to low energy regions and then moved up gradually to higher and higher energy regions. This device also enables one to stop the search for larger molecules after chemically significant low energy conformers have been exhaustively found.[5,6,7]

The new algorithm mentioned above has been implemented into a program CONFLEX3.[8] The present version (v 3.2) uses MM2(77) as the minimizer.[9] Recently MM2 has been modified to MM3 [10] Numerical details of the present results will change slightly if one uses MM3. However, our conclusions will not be dependent on the force field. After a search job is finished, all of the conformers obtained are subjected to re-optimization with MM2 force field and the full-matrix Newton-Raphson method implemented in BIGSTRN3[11] in order to check if any of them will show significantly large negative eigenvalues in their force constant matrices. The recalculations also allow us to estimate relative free energies of conformers by taking into accounts of vibrational and symmetry contributions to the partition function. Because MM2 force field is not calibrated for vibration, the accuracy of the calculated free energy cannot be assessed.[12] All the calculations have been carried out on a HP Apollo DN10000 workstation.

RESULTS AND DISCUSSION

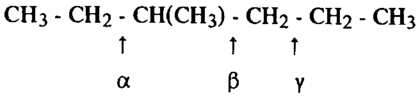
Asymmetric deformation in GG' segment

Total numbers of conformers (N_{obs}) obtained are given in the third column of Table 1, where conformations are identified without considering redundancy due to symmetry, namely the number of conformers are presented for the asymmetric linear chain molecules (*e.g.* 1 for a C_6-chain). N_{obs} increases from 11 of *n*-pentane to 35, 109, 347, 1101 and 3263 of *n*-decane. Let us note here that, contrary to the conventional idea,[13] these numbers are all considerably larger than 3^n (the fourth column of Table 1). This discrepancy could have actually been anticipated from the recent conformation that a GG' segment is asymmetrically deformed to produce two energy minima.[2,14] We will first focus our attention on the overlooked aspect of high energy conformations in some detail.

Table 1. Total Number of Conformations (N), and Ratio of GG'-Containing to GG'-free Conformations (R)

n[a]	corresp *n*-alkane[b]	CONFLEX3	3^n	CONGAU[d]				$N_{GG'}$[i]	R[j]
		N_{obs}[c]		N_{init}[e]	N_{forb}[f]	N_{calc}[g]	N_o[h]		
2	pentane	11	9	11	0	11	7	4	0.57
3	hexane	35	27	37	2	35	17	20	1.17
4	heptane	109	81	125	16	109	41	84	2.04
5	octane	347	243	423	76	347	99	324	3.27
6	nonane	1,101	729	1,431	(350)[k]	(1,081)	239	1,192	4.99
7	decane	3,263	2,187	4,841	(1,406)[k]	(3,435)	577	4,264	7.39
8	undecane	—	6,561	16,377	(3,013)[k]	(13,364)	1,393	14,984	10.76
9	dodecane	—	19,683	55,403	—[l]	—	3,363	52,040	15.47
10	tridecane	—	59,049	187,427	—[l]	—	8,119	179,308	22.08

[a] Number of internal C-C bonds along back-bone chain whose rotation angles are restricted to A, G and G' Bonds containing methyl groups are not counted. [b] Corresponding *n*-alkane. [c] Number of conformers found by exhaustive search using CONFLEX3. The data on *n*-pentane and *n*-hexane are taken from ref 2. Duplication due to symmetry has been neglected See text. [d] A small Fortran program for counting the number of conformational isomers M. Yamato, B A. Thesis, TUT, 1991 [e] Number of conformations initially counted by CONGAU without taking into accounts of 'forbidden' conformations. [f] Number of forbidden conformations [g] Final number of predicted conformation. $N_{calc}=N_{init} - N_{forb}$ [h] Number of GG'-free conformations counted by CONGAU [i] $N_{GG'}=N_{init} - N_o$, number of conformations containing at least one GG' segment without considering forbidden conformations [j] $R=N_{GG'}/N_o$ Ratio of GG'-containg to GG'-free conformations [k] Not exact See text [l] The present version of CONGAU cannot handle this size



$$\underset{}{CH_3} - \underset{\underset{\alpha}{\uparrow}}{CH_2} - CH(CH_3) - \underset{\underset{\beta}{\uparrow}}{CH_2} - \underset{\underset{\gamma}{\uparrow}}{CH_2} - CH_3$$

1

The conformation having a GG' segment has never been observed experimentally, but their instability has been long anticipated.[15] Back in 1966, Abe and others[16] had already realized from simple empirical energy calculations that a peculiar deformation occurred in a GG' segment to relieve the high strain: one of the gauche bonds rotated to ±115° while the other bond remained at a normal rotation angle near ∓60° (pentane effect).[15] More recently, these computed results are *confirmed* by the *ab initio* gradient geometry-optimization calculations using 6-31G* basis set of *n*-pentane and *n*-hexane to give asymmetric energy minima having bond rotation angles of ±63° and ∓95° in GG' segment (Figure 1). Calculations at the MP4SDQ/6-31G*//HF/6-31G* level predict that these local minima (enantiomeric pair) are 3.3 kcal/mol less stable than the AA segment.[2] MM2 calculations gave almost identical geometry and relative energy (3.2 kcal/mol).[2,17,18]

C_5-chain

Henceforth, for an asymmetric C_5-chain, there should be eleven distinct conformers: AA, AG, AG', GA, G'A, GG, G'G', **GG'**, **G** G', G'**G** and **G'**G. Bold face indicates that the bond has an abnormally wide dihedral angle (±95°). In n-pentane, GG' forms consist of an enantiomeric pair. According to the *ab initio* calculations mentioned above, they populate 0.5% of the whole mixture of rotamers at room temperature in the gas phase.

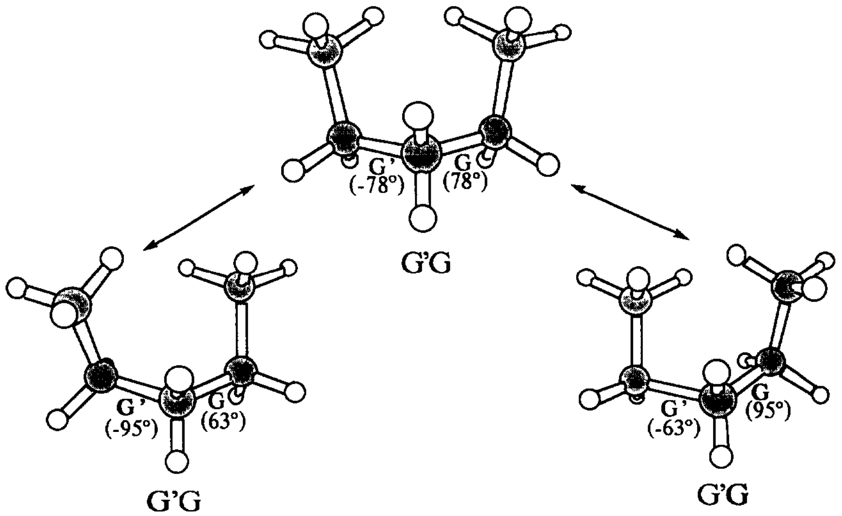


Figure 1. Three conformations of consecutive gauche bonds of opposite sign (n-pentane used as model). GG' and GG' are energy-minima, whereas GG' is the saddle point.

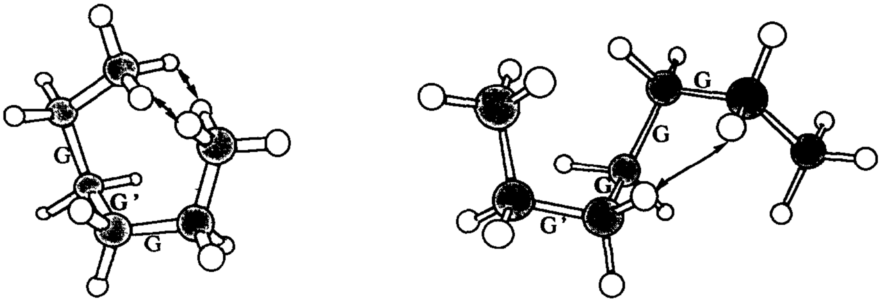
C_6-chain

It has also been noted in our previous report[2] that molecules containing a GG' segment, XGG'Y, give rise to two distinct energy minima (not enantiomers), XGG'Y and XGG'Y, when X and Y are different. This means that the number of conformations at least doubles for every occurrence of a GG' segment. For example, molecule 1 having six-carbon backbone with three rotatable internal bonds (α, β and γ) should produce more than 3^3, namely 27 conformers:

AAA	(no gauche bond)							
GAA	G'AA	AGA	AG'A,	AAG	AAG'	(one gauche)		
GGA	G'G'A	AGG	AG'G'	GG'A	G'GA	AGG'	AG'G	
GG'A	G'GA	AGG'	AG'G	GAG	GAG'	G'AG	G'AG'	(two gauches)
GGG	G'G'G'	GGG'	G'GG	GG'G	GG'G'	G'G'G'	G'G'G	
GGG'	G'GG	GG'G	GG'G'	G'GG'	G'G'G	(three gauches)		

We have reported that the GG'G (and G'GG', boxed above) structure, which has two overlapping GG' segments, could not be geometry-optimized but spontaneously transforms itself into GAG when 6-31G*, MM2 and MM3 were used as the minimizer.[2] As shown in Figure 2, the GG'G conformation involves extremely close contact between protons on 1/6 carbon atoms We will hereafter call such an un-optimizable conformations as 'forbidden'. Therefore, for molecules like 1, it is very likely that the total number of conformer will be 35 (see N_{calc} of Table 1, the line for n=3).

In *n*-hexane, the total number of *unique* conformers is twelve.[2] Among these, five highest-energy conformers contain at least one GG' sequence and these GG'-containing conformers populate a total of 1.0% at



GG'G GGGG'

Figure 2. Two 'forbidden' partial conformations of alkyl chain, GG'G and GGGG', modeled by n-hexane and n-heptane, respectively. Close H/H contacts (arrowhead) are the cause of destabilization. Un-optimized structures.

room temperature based on our previous *ab initio* free-energy calculations.[2] The contribution of GG'-containing conformation in the chemically significant conformational space is not very high but still not quite low as to be negligible even for such a small molecule as *n*-hexane.

C_7-chain

With these observations in mind, let us analyze C_7-chain (*n*-heptane) in some detail. This length of chain provides considerably complicated but still manageable situation (Table 2). When all possible combinations of rotation indices for the four internal C-C bonds are generated manually, taking into accounts of the GG' asymmetry, 125 such combinations emerge (see also Table 1, N_{init} for heptane). When the four-letter symbols are grouped into redundant pairs that are related by 180°-rotation or mirror reflection, 35 unique conformations remain for *n*-heptane (Table II). It may be mentioned here that a textbook states that *n*-heptane has 13 unique conformers.[19] In Table 2, the straining GG' segment first appears at the 14th rank, and all the rotamers below this rank contain at least one GG' segment.

Execution of CONFLEX3.2 program under the exhaustive search mode gave most of the expected 125 conformers, but sixteen of them are missed (No. 32-35 multiplied by statistical weights). Among the MM2-optimized geometries of n-heptane rotamers, absolute values of gauche angles (G and G') range between 55.9 and 73.0°, while those of abnormal gauche angle (G and G') fall within 88.9 and 104.3°. Two extreme values of G and G' appear in conformer No. 30. For example, dihedral angles are 63.23, -88.96, -63.12 and 104.32° for GG'G'G. The missed conformations were thereafter prepared manually and confirmed to be un-optimizable. Twelve of these (No.32, 34, 35) have the forbidden conformation of the type GG'G. The remaining four (No. 33) do not have this segment, but a closer look at the model of GGGG' conformation (Figure 2) indicates that this conformation produces impossibly close H/H contact between 2/5 carbon atoms, thereby presenting a new forbidden segment pattern in *n*-alkane.

Table 2. *n*-Heptane Conformations and Their Calculated Distribution (MM2)

			CONFLEX/MM2			
No[a]	repres conf[b]	statis wt[c]	SE[d] kcal/mol	ΔG_{298}[e] kcal/mol	$\Delta\Delta G_{298}$ kcal/mol	Bolz dis[f] %
1	AAAA	1	4.1045	102.7747	0.0000	30.6701
2	AAAG	4	4.9865	102.9191	0.1444	24.0325
3	AAGA	4	5.0240	102.9527	0.1780	22.7067
4	AAGG	4	5.6912	104.0176	1.2429	3.7589
5	AGGA	2	5.7087	104.4630	1.6883	1.7716
6	AGAG	4	5.8343	103.8964	1.1217	4.6127
7	GAAG	2	5.8485	104.2846	1.5099	2.3945
8	GAAG'	2	5.8816	104.2803	1.5056	2.4120
9	AGAG'	4	6.0367	103.9652	1.1905	4.1067
10	AGGG	4	6.3813	105.1094	2.3347	0.5946
11	GAGG	4	6.4466	104.8922	2.1175	0.8581
12	GAG'G'	4	6.7091	105.0571	2.2824	0.6495
13	GGGG	2	7.0910	106.5694	3.7947	0.0505
14 a	AAGG'	4	7.2914	105.4663	2.6916	0.3254
15 a	AAGG'	4	7.2996	105.4914	2.7167	0.3119
16	AGG'A	4	7.3282	105.5430	2.7683	0.2859
17 b	AGGG'	4	7.9269	106.5928	3.8181	0.0485
18 c	AGG'G'	4	8.0407	106.6565	3.8818	0.0436
19 d	GAGG'	4	8.0848	106.3157	3.5410	0.0775
20 d	GAGG'	4	8.1108	106.4161	3.6414	0.0654
21 e	GAG'G	4	8.1953	106.5245	3.7498	0.0545
22 b	AGGG'	4	8.3389	106.5561	3.7814	0.0517
23 c	AGG'G'	4	8.3574	106.5931	3.8184	0.0485
24 e	GAG'G	4	8.3715	106.5791	3.8044	0.0497
25 f	GGGG'	4	8.7327	107.6638	4.8891	0.0080
26	GGG'G'	4	8.9587	107.8368	5.0621	0.0059
27 g	AGG'G	4	9.5413	108.2269	5.4522	0.0031
28 h	GG'G'G	2	9.8950	109.0203	6.2456	0.0008
29 i	GGG'G	4	10.6430	109.2994	6.5247	0.0005
30 h	GG'G'G	4	10.8246	109.3282	6.5535	0.0005
31 h	GG'G'G	2	10.8302	110.0448	7.2701	0.0001
32 g	AGG'G[g]	4	——	——	——	——
33 f	GGGG'[g]	4	——	——	——	——
34 i	GGG'G[g]	4	——	——	——	——
35	GG'GG'[g]	4	——	——	——	——
	Sum	125				

[a] If a pair of conformations have the same alphabetical index in bold face, they are isomers arising from asymmetric deformation in the GG' segment. [b] Representative conformation. Only one notation is given for a set of symmetrically equivalent conformers. [c] Statistical weight. The number of conformers which become identical by 180°-rotation or mirror reflection. [d] MM2 steric energy [e] Free energy, see Computational Methods section. [f] Boltzmann distribution of unique conformers based on free energy difference calculated at 25°C. [g] Not an energy minimum on MM2-energy surface.

When two GG' segments are linked with the same sign, like in GG'G'G (No. 28, 30 and 31), they behave independently to each other within the framework of MM2. For this reason, there are eight conformers for the GG'G'G form. Thus, for any chain consisting of seven non-equivalent carbons, there are 109 conformers on the MM2 energy surface, and for symmetric structure like *n*-heptane, there are 31 unique conformers. Relevant to our present concern is the observation that the sum of population of the GG'-contains conformers (No. 14 to 31) amounts to 1.38%.

Programmed counting of the number of conformations

Beyond C_7-chain, the conformational flexibility is such that the manual analysis as given in Table 2 gets out of reach. Hence, based on the experience up to C_7-chain, we wrote a small program CONGAU which gives rotamers for a linear chain molecule having n internal C-C bonds by the following steps:

(1) Generate 3^n combinations of n successive letters from A, G and G'.

(2) When GG' or G'G appears, duplicate the conformation by giving bold face to G and G' alternately.

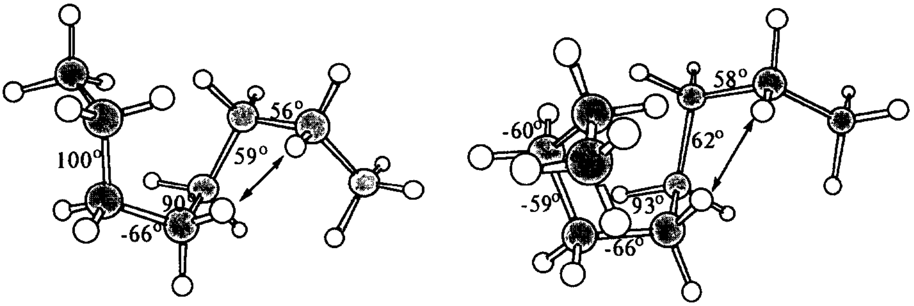
(3) When the GG' or G'G is followed by G or G' so that alternating GG' block is formed (*e.g.*, GG'GG' ···), simply give bold faces alternately to give only two conformations.

(4) Detect the two types of forbidden conformations (GG'G and GGGG') by examining all partial segments to remove them.

The results of running the program for n up to ten are included in Table 1 (column under CONGAU), and shows how the GG' segment affects the distribution of conformations in the conformational energy space. N_{init} is obtained by considering only the asymmetric GG' segment. N_{calc}, an estimate of the total number of conformer, is obtained by subtracting the total number of forbidden conformers (N_{forb}) from N_{init}.

Comparison of the results of CONFLEX calculations with the output of CONGAU revealed new complications: two conformers, GGGG'G-octane and GGGG'G'G'-nonane turned out to be energy-minima, despite the presence of forbidding GGGG' element (underlined, see Figure 3). Examination of the optimized geometries of the former revealed that the severe C2/C5 contact could not be fully relieved (rotation of C3-C4 bond may lead to an increased congestion between protons at C3 and C7 for octane and C3 and C8 for nonane) as in the GGGG'-heptane, and that the geometry-optimization process compromised at a high local energy minimum. A similar explanation applies to the latter.

The predicted number of conformers (N_{calc}) agrees with that of N_{obs}, the total number of geometry-optimized conformers obtained by the exhaustive search with CONFLEX3, for *n*-heptane and *n*-octane, but not completely for *n*-nonane (predicted 1,081, observed 1,101) and *n*-decane (3,435 vs. 3,263). Clearly, thereshould be more forbidding patterns and exceptions for the longer chains. However, we stopped further examination of these insignificant conformations any more. Even if we were able to set up elaborate rules to



GGGG'G GGGG'G'G'

Figure 3. Allowed conformations despite the presence of forbidden partial segments. Energy-minimized structures.

predict forbidden and patterns and their exceptions for the gauche-rich conformations, they will be dependent on the particular empirical force field used and perhaps work only for a linear chain. For this reason, the values of N_{calc} for alkanes with n greater than six are uncertain (hence parenthesized in Table 1).

Notwithstanding, a trend is clear that the total number of conformers for the longer chain molecules will be considerably greater than 3^n. One of the interesting observations in this work is that the rapid increase in the number of conformers (N_{obs} or N_{calc}) with the chain length is largely due to the increase in the GG'-containing, hence chemically uninteresting conformations. $N_{GG'}$, the number of such conformers is obtained by subtracting N_0, the number of conformers not containing GG' segment at all, from N_{calc}. As shown in Table I, the ratio of GG'-containing to GG'-free conformations (R) increases rapidly with n For n≥8, more than 90% of the whole conformations are expected to contain at least one GG' segment. However, because of their high strain, the free energy contribution of GG'-containing conformations in the longer chain will never exceed a few %

Table I also reveals an interesting and encouraging feature: the total number of GG'-free conformers (N_0), or most of the low-energy conformers, increases only by an exponent of 2.4 to n These observations lead to a conclusion that an algorithm which restricts the search to the low-energy regions will make it possible to exhaustively generate chemically significant conformers, GG'-free plus a few % of GG'-containing, even for considerably large molecules within reasonable computer time.

PERSPECTIVE

Beyond C_{11}-chain, the values of N_{calc} are predicted to exceed ten-thousands and quickly will become out of control with regard to computing time and memory size. However, these physical boundaries are being loosened quickly with the unexpectedly rapid progress in hardware.

If one completely ignores the contribution of GG'-containing conformers, it would be an easy task to produce all of N_0 structures by any molecular modeling software and geometry-optimize them by any conventional computational method, if it is not too large and complicated. However, for those types of work which cannot ignore the few percent of error, or for those types of compounds having such complex patterns of substituents that a straightforward prediction of the GG'-free conformers would be difficult, program CONFLEX will be useful.

High flexibility of the chain structure is demonstrated impressively by comparing the total number of conformers with that of the ring structure having the same number of carbon atoms: C_9-chain (1,081, N_{calc} in Table I) *vs* C_9-ring (162); C_{10}-chain (3,534) *vs* C_{10}-ring (360); C_{11}-chain (16,377) *vs* C_{11}-ring (880); C_{12}-chain (55,403) *vs* C_{12}-ring (2,664). Because we are dealing here with asymmetric rings, the number of ring conformations are obtained by multiplying 2n (in this case n is the number of ring atoms) with the number of conformers for cycloalkanes reported.[20] Chain conformers are by one digit more abundant than ring conformers. Considering the fact that C_{12}- to C_{17}-rings are almost the largest limit for the exhaustive search by the random method,[20,21] it must be concluded that the latter method would be highly unfavorable for longer chain structures. The probability of finding a low-energy conformer should be approximately proportional to 1/R in the random method, and this rate decreases quickly as the chain length increases (Table 1).

CONCLUSIONS

(1) The conformational energy surface of an open-chain molecule is more complex than previously thought, primarily as the consequence that a GG' segment deforms in two directions leading to two distinct energy minima.

(2) Within the framework of MM2, the total numbers of conformers have been established for small *n*-alkanes up to *n*-decane From *n*-undecane and above, the number will exceed ten-thousand, and increase exponentially and, considerably more rapidly than 3^n.

(3) Fortunately, the distribution is biased heavily towards insignificantly high-energy region and the number of low-energy conformers increases only by a power of only 2.4 to n.

(4) For this reason, the computer search of low-energy region in the conformation space can be effectively carried out for flexible open chain molecules. Our program can be useful for this purpose.

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