Enumeration of the Conformers of Unbranched Aliphatic Alkanes

Gyula Tasi,*,†,‡ Fujio Mizukami,† István Pálinkó,§ József Csontos,‡ Werner Győrffy,‡ Padmakumar Nair,† Kazuyuki Maeda,† Makoto Toba,† Shu-ichi Niwa,† Yoshimichi Kiyozumi,† and Imre Kiricsi‡

Department of Surface Chemistry, National Institute of Materials and Chemical Research, 1-1 Higashi, Tsukuba, Ibaraki 305-8565, Japan, Applied Chemistry Department, József Attila University, Rerrich B. tér 1, H-6720 Szeged, Hungary, and Department of Organic Chemistry, József Attila University, Dóm tér 8, H-6720 Szeged, Hungary

Received: April 15, 1998; In Final Form: June 8, 1998

An effective one-electron quantum chemical method was applied to enumerate the conformers of unbranched aliphatic alkanes. The results obtained for butane, pentane, hexane, and heptane were utilized to derive four rules with which the number and sequences of the existing conformers up to undecane could be reproduced. The validity of the rules was confirmed at Hartree−Fock and second-order Moeller−Plesset levels too. Full ab initio conformational analyses were performed for the butane, pentane, hexane, heptane, and octane molecules. The rules demonstrate that the most important factors governing the conformational behavior of unbranched aliphatic alkanes are the nonbonded repulsive−attractive (van der Waals) interactions between the hydrogen atoms attached to the carbon atoms at positions 1,4; 1,5; 1,6; and 1,7. The calculated gas-phase standard heats of formation of the unbranched aliphatic alkanes closely matched the experimental values.

Introduction

Theoretical study of the conformational flexibility of biologically active molecules is of utmost importance. A knowledge of each possible conformer is essential, since it is far from certain that the biologically active conformer corresponds to the global minimum of the molecular potential-energy surface. The conformational flexibility of molecules with potential pharmacological activity must also be taken into account in similarity studies.[1]

The simplest class of molecules with high conformational flexibility is the unbranched aliphatic alkanes. Despite numerous studies[2−4] and even books[5] on this topic, it is still not clear how many conformers exist for the individual members of this homologous series. According to Tsuzuki et al., the number of possible conformers is probably larger than 3^n, where n is the number of the rotatable C−C bonds (i.e., the number of free C−C−C−C torsional angles).[3]

The following methods can be applied to study the conformational properties of large molecules: molecular dynamics, molecular mechanics, and semiempirical quantum chemistry. Molecular mechanics and dynamics methods provide results quickly, but the results are generally less reliable than those of the traditional quantum chemical methods. However, an appreciable number of examples demonstrate that even the widely used semiempirical quantum chemical methods do not always provide satisfactory results. For instance, the AM1 method[6] cannot reproduce the conformational spectrum of α,α'-diaminoacetone, and its suitability for investigating the conformational properties of oligopeptides is therefore questionable.[7] It has recently been shown that the MNDO[8] and AM1 methods overestimate the stabilities of the all-trans conformers of unbranched aliphatic alkanes.[4] It has also been suggested that large molecules must be taken into consideration on the parametrization of new semiempirical methods, since the AM1 and PM3[9] standard heats of formation for large ring systems are clearly not satisfactory.[10]

We recently studied the ground-state equilibrium molecular geometries and permanent electric dipole moments of aliphatic hydrocarbons.[11] Accurate molecular total energies and zero-point vibrational energy (ZPVE) corrections were additionally obtained by the Gaussian-2 (G2) method[12] for several aliphatic alkane molecules.[13] On the basis of these results, we parametrized an effective one-electron quantum chemical model for aliphatic alkanes.[13] The method was named the scaled effective one-electron method (SEOEM). For aliphatic alkane molecules, the SEOEM gas-phase standard heats of formation closely matched the experimental values. For 63 molecules, the average absolute deviation and maximum absolute deviation were 0.83 and 3.70 kcal/mol, respectively.[13]

In this work, SEOEM model quantum chemistry is applied to investigate the conformational properties of unbranched aliphatic alkanes. For the butane, pentane, hexane, heptane, and octane molecules, full ab initio conformational analyses were performed at Hartree−Fock (HF) and second-order Moeller−Plesset (MP2) levels.

Theoretical Background

The SEOEM model takes into consideration all the electrons of the system (all-electron method).[13] For the calculation of molecular integrals and their derivatives, the STO-3G basis set is used for aliphatic alkanes. The details of the parametrization and the optimized parameters of the SEOEM model for aliphatic alkanes can be found elsewhere.[13]

To calculate the ZPVE corrections within the SEOEM approximation, the harmonic vibrational frequencies are used

---

[†] National Institute of Materials and Chemical Research.

[‡] Applied Chemistry Department, József Attila University.

[§] Department of Organic Chemistry, József Attila University.

S1089-5639(98)01866-0 CCC: $15.00

without scaling. For evaluation of the enthalpies of formation of molecules, the same procedure is applied as within the G2 approximation.[14] The thermal corrections to the enthalpies of molecules are calculated as follows: $^3/_2$RT for translation, $^3/_2$RT for rotation (nonlinear molecules), the vibrational term from the harmonic vibrational frequencies, and the *PV* term (*RT*), which converts energy to enthalpy. The electronic and nuclear partition functions are set to unity, as usual, and their contributions are therefore ignored. For calculation of the standard heat of formation, the low-frequency torsional vibrations are regarded as free internal rotations. The cutoff value of 260 cm^{-1} was obtained from the literature.[15]

Software Packages

The ab initio calculations were performed with the Gaussian 94 package[16] on CRAY C90 and IBM SP2 computers. The initial geometries were prepared and the results were evaluated on a PC with the PcMol package.[17]

The SEOEM calculations were performed with the SEHMO program[18] on CRAY C90, IBM SP2, and personal computers. For searching local minima in the conformational space, quasi-Newton and conjugate gradient methods were used.

For the enumeration of different conformers of unbranched aliphatic alkanes, a FORTRAN program (ENUMERAT) was written. The program can generate MOPAC,[19] Gaussian 94, MM2,[20] and SEHMO input files for the conformational analysis of any unbranched aliphatic alkane. It is also possible to perform constrained generation, i.e., some torsional angles can be fixed. With the help of structural similarity calculations, the unique (nonisomorphic) conformers of *n*-alkanes can be determined. This program is available from the authors upon request.

Results and Discussion

The SEOEM model was used first to find the conformers of the pentane, hexane, and heptane molecules. The initial geometries were generated via the Monte Carlo method: the free C−C−C−C torsional angles were chosen between 0 and 2π in a random manner. Pentane, hexane, and heptane molecules have two, three, and four rotatable C−C bonds, respectively. The number of trial geometries was increased stepwise between 100 and 3000 until the number of local minima (i.e., the number of conformers) obtained became stable. Harmonic vibrational analysis was performed for each stationary point. In this way, some of them proved to be saddle points. After the attainment of a certain number of initial geometries, only the number of saddle points increased. The SEOEM model provided 11, 35, and 107 conformers for the pentane, hexane, and heptane molecules, respectively.

Figure 1 displays the SEOEM conformational map of the pentane molecule. The figure clearly shows the local minima and the transition states connecting them. The numbers of local minima, transition states, and local maxima are 11, 20, and 4, respectively. It is also clear that there are two kinds of gauche C−C−C−C torsional angles: one is around ±60° and the other around ±95°. Let us introduce the following symbols for the various torsional angles: t, ∼180°; g+, ∼+60°; g−, ∼−60°; x+, ∼+95°; x−, ∼−95°. Several of the conformers of pentane have the same total energy: tg+ = tg− = g+t = g−t, g−g− = g+g+ and x−g+ = x+g− = g+x− = g−x+. The transition state connecting the conformers g+x− and x−g+ is usually designated g+g− in the literature. This is not correct, however, since the torsional angles in the transition state (+75.6, −75.6) are very different from those of the conformers [g+x−, (+60, −95); x+g−, (+95, −60)]. The transition state has C_s point group symmetry. All this holds true for the transition state between the conformers g−x+ and x+g−. The SEOEM results reveal that 3^n is a lower limit and 5^n is an upper limit for the number of conformers, where *n* is the number of free C−C−C−C torsional angles.

The geometries of the conformers obtained by the SEOEM model were then fully optimized at the HF (RHF/6-31G*) and MP2 (RMP2(FC)/6-311G**) levels. FC (frozen core) in parentheses means that the inner shell electrons were excluded from the electron correlation (post-HF) calculations. Every SEOEM local minimum proved to be a local minimum at HF and MP2 levels too. The initial geometries were very close to the HF and MP2 equilibrium geometries, and each geometry optimization therefore terminated quickly. Deviations of the SEOEM and HF equilibrium geometries from the MP2 ones are to be seen in Figures 2 and 3 for the pentane and hexane molecules, respectively. The rmsd (root-mean-square distance) data were calculated as

$$\mathrm{rmsd} = \left(\frac{\sum_{i=1}^{m} \Delta_i^2}{m}\right)^{1/2} \qquad (1)$$

In eq 1, the data Δ_i give the minimum distances between the corresponding fitted atoms in the moving and in the reference molecule; *m* is the number of atomic pairs fitted. Every atom in each molecule was selected for fitting. It is to be seen that the SEOEM geometries are better than the RHF/6-31G* ones.

According to the upper limit 5^n, 25, 125, and 625 geometries were then generated for the pentane, hexane, and heptane molecules, respectively. After elimination of the previously determined geometries (local minima), 14, 90, and 518 full geometry optimizations were performed at HF and MP2 levels for the pentane, hexane, and heptane molecules, respectively. New local minima were not obtained, but some saddle points became accessible.

It is clearly seen that for the pentane, hexane, and heptane molecules, the results of the HF, MP2, and SEOEM calculations are in complete accordance.

The results of the conformational analyses of butane, pentane, hexane, and heptane allow us to establish some simple rules for the sequences of the existing conformers. These are as follows. (1) The double sequences x+x−, x−x+, g+g−, and g−g+ are forbidden. (2) The triple sequences g+x−g+, g−x+g−, x+g+x−, x−g+x+, x+g−x−, and x−g−x+ are likewise not allowed. (3) The quadruple sequences x+g−g−x+ and x−g+g+x− are forbidden. (4) x+ needs g−, such as ...x+g−... or ...g−x+...; similarly, x− needs g+, such as ...x−g+... or ...g+x−.... These rules exactly reproduce all the existing conformers of the butane, pentane, hexane, and heptane molecules.

The question now arises of whether these rules can be applied to longer *n*-alkanes or not. Table 1 presents data relevant to this question for the C_4−C_{12} unbranched aliphatic alkanes. For the octane, nonane, decane, and undecane molecules, the initial geometries for the SEOEM calculations were generated in three ways: (i) via the Monte Carlo method in a random manner (10000−200000 starting points), (ii) according to the upper limit 5^n, and (iii) via the rules 1−4. The three procedures gave the same results as far as the number of conformers and their sequences are concerned (see the last column of Table 1). These facts strongly suggest that rules 1−4 have wide validity. The numbers in parentheses in Table 1 are the numbers of the

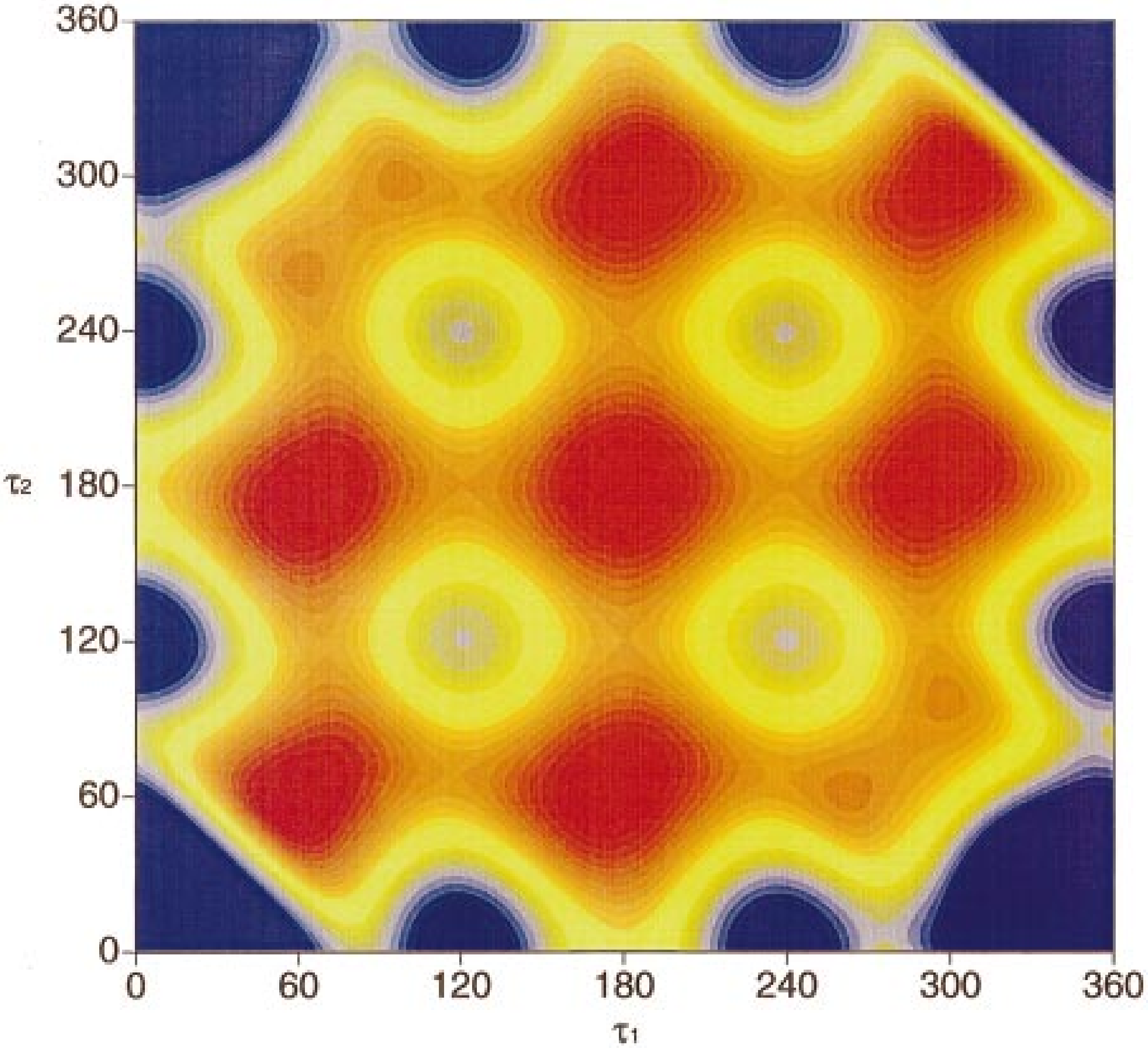

Figure 1. SEOEM conformational map of pentane.

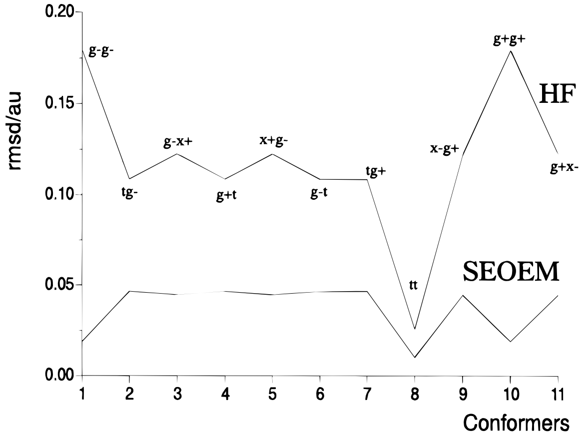

Figure 2. The rmsd deviations of the equilibrium molecular geometries determined by quantum chemical methods from the reference geometries of the conformers of pentane.

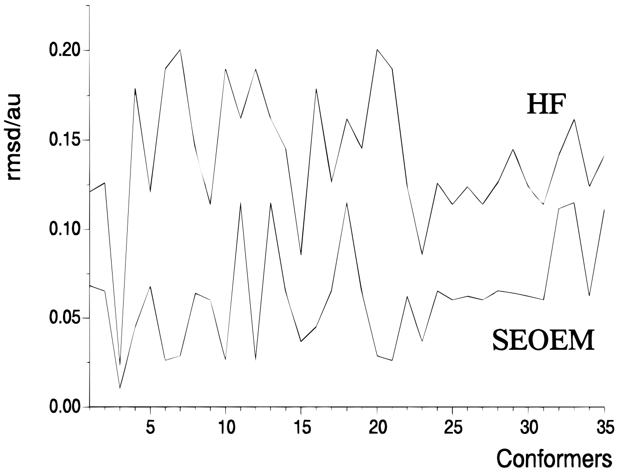

Figure 3. The rmsd deviations of the equilibrium molecular geometries determined by quantum chemical methods from the reference geometries of the conformers of hexane.

structurally unique (nonisomorphic) conformers. They were obtained by structural similarity calculations using the sequences of the conformers.

Gotō et al. have applied the MM2 molecular mechanics force field to determine the number of possible conformers of *n*-alkanes up to decane.[21] For pentane, hexane, heptane, octane, nonane, and decane, the numbers of the found conformers were 11, 35, 109, 347, 1101, and 3263, respectively.[21]

When our rules are applied, excluding the third one, the numbers of the conformers for these molecules would be 11, 35, 109, 347, 1105, and 3507, respectively. It is to be seen

TABLE 1: Number of Possible Conformers of Unbranched Aliphatic Alkanes (*n*: Number of Rotatable C−C Bonds)[a]

molecules	*n*	3^n	5^n	rules 1−4	found
butane	1	3	5	3 (2)	3 (2)
pentane	2	9	25	11 (4)	11 (4)
hexane	3	27	125	35 (12)	35 (12)
heptane	4	81	625	107 (30)	107 (30)
octane	5	243	3125	339 (95)	339 (95)
nonane	6	729	15625	1073 (279)	1073 (279)
decane	7	2187	78125	3375 (876)	3375 (876)
undecane	8	6561	390625	10633 (2691)	10633 (2691)
dodecane	9	19683	1953125	33525 (8481)	

[a] The numbers in parentheses are referring to the nonisomorphic conformers.

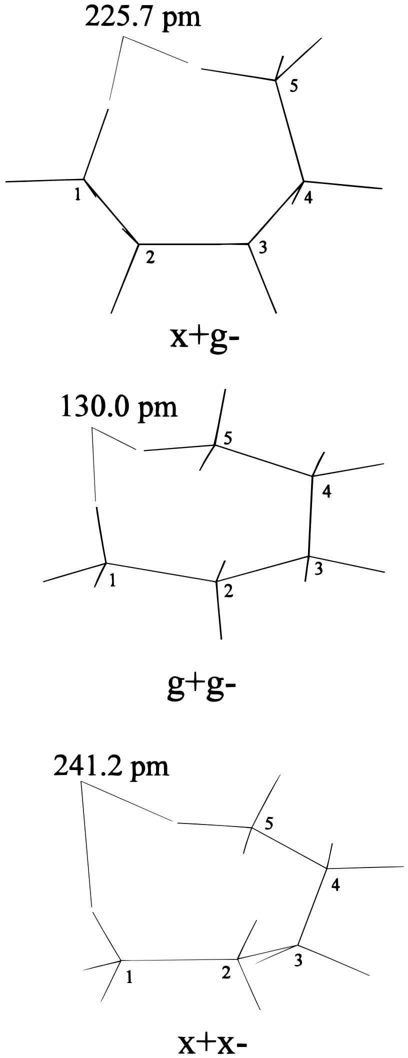

Figure 4. Geometries of some allowed and forbidden sequences of pentane.

that the numbers corresponding to heptane and octane are exactly the same. For nonane and decane, the differences are 4 and 244, respectively. On the basis of these results, one can assume that the structures containing the sequences x+g−g−x+ and x−g+g+x− might be local minima on the MM2 potential-energy surfaces. To prove this assumption, for the heptane and octane molecules, conformational analyses were performed at MM2 level. These calculations verified the existence of the structures under consideration (heptane, x+g−g−x+ and x−g+g+x−; octane, tx+g−g−x+, tx−g+g+x−, g+x+g−g−x+, g−x−g+g+x−, x+g−g−x+t, x+g−g−x+g+, x−g+g+x−t, and x−g+g+x−g−) on the MM2 potential-energy surfaces. However, these sequences are not local minima for the heptane and octane molecules at the SEOEM, HF, and MP2 levels. For the heptane molecule, they unambiguously proved to be transition states on the SEOEM and MP2/6-31+G* potential-energy surfaces. To be absolutely sure, a full ab initio conformational analysis was performed at the HF level for the octane molecule. This analysis resulted in 95 nonisomorphic conformers in complete accordance with rules 1−4. To sum up, the results obtained at the SEOEM, HF, and MP2 levels clearly prove that rules 1−4 are valid and the numbers of possible conformers are smaller than those predicted by the MM2 method. However, it is noteworthy that rules 1, 2, and 4 are valid at the MM2 level too.

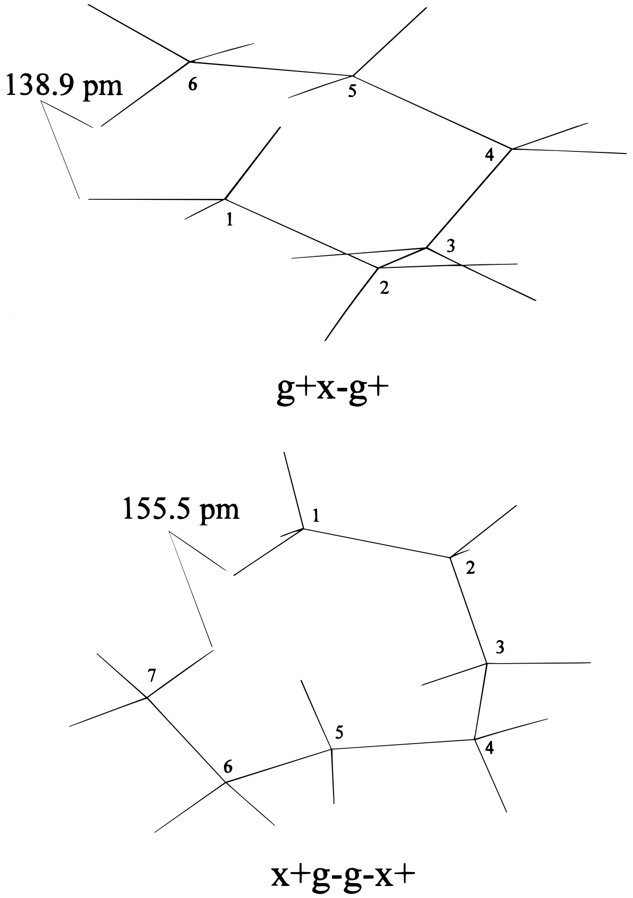

Figure 5. Geometries of some forbidden sequences of hexane and heptane.

For a better understanding of rules 1−4, let us examine the geometries of some forbidden sequences. Figure 4 displays the MP2 equilibrium geometry of the conformer x+g− and the fictitious geometries of the forbidden sequences g+g− and x+x− of pentane. For the conformer x+g−, the minimum distance between the hydrogen atoms attached to C(1) and C(5) is 225.7 pm. For the forbidden sequences g+g− and x+x−, the distances are 130.0 and 241.2 pm, respectively. For the first forbidden sequence, there is a net van der Waals repulsion (1,5 repulsion), while for the second one, there is a net van der Waals attraction (1,5 attraction) between the terminal methyl groups. (The same conclusion may be reached via the experimental van der Waals radius of the hydrogen atom, 118.5 pm.) For longer chains, similar 1,5 attraction−repulsion effects may appear between the groups $-CH_3$ and $-CH_2-$ or $-CH_2-$ and $-CH_2-$.

Figure 5 displays the fictitious geometries of the forbidden sequences g+x−g+ and x+g−g−x+ of the hexane and heptane

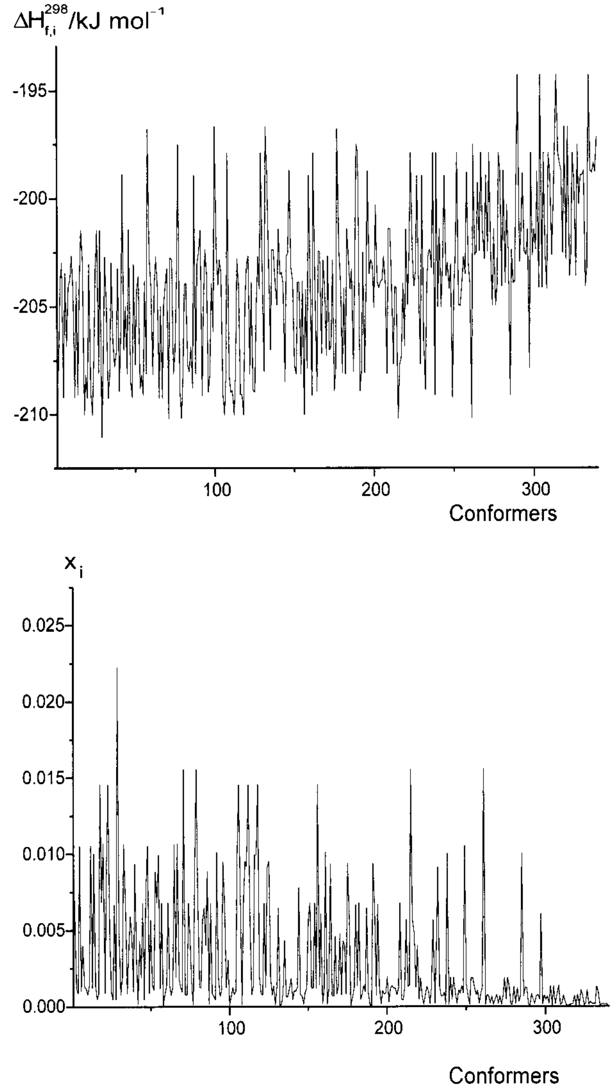

Figure 6. SEOEM standard heats of formation and populations of the conformers of octane.

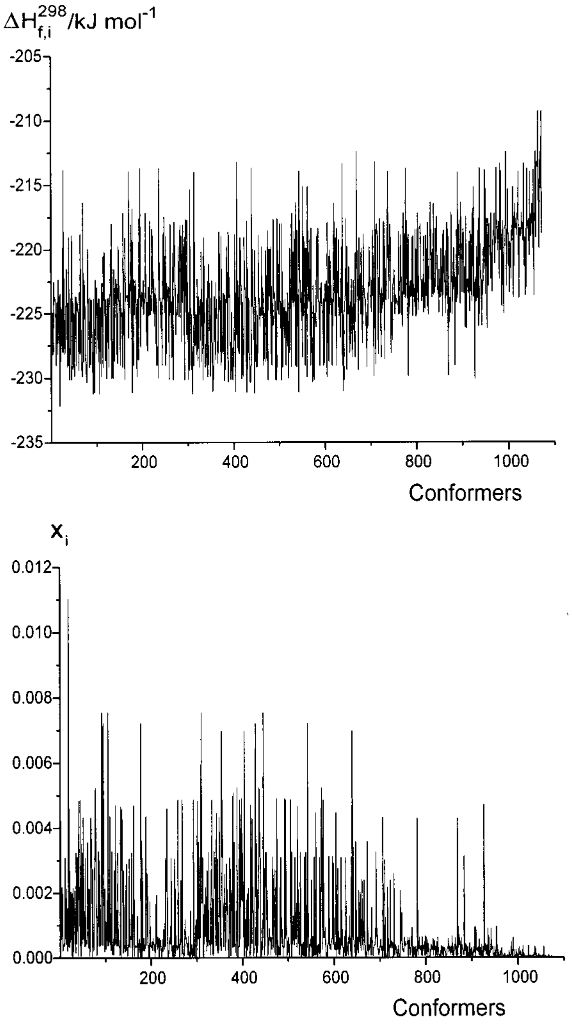

Figure 7. SEOEM standard heats of formation and populations of the conformers of nonane.

molecules, respectively. In both cases, there is a net van der Waals repulsion between the terminal methyl groups, 1,6 in the first case and 1,7 in the second case. The minimum distances between the relevant hydrogen atoms are 138.9 and 155.5 pm, respectively. For longer chains, 1,6 and 1,7 repulsion interactions may appear between the groups $-CH_3$ and $-CH_2-$ or $-CH_2-$ and $-CH_2-$.

Similar studies reveal that the nonexistence of the sequences g+x+, g−x−, x+g+, and x−g− is due to 1,4 repulsion, that of the sequences tx−, tx+, x−t, x+t, x−x−, and x+x+ is due to 1,4 attraction, and that of the sequences x+x− and x−x+ is due to 1,5 attraction.

To summarize, it can be stated that the number and sequences of the conformers of unbranched aliphatic alkanes are determined by the nonbonded repulsive−attractive (van der Waals) interactions of the hydrogen atoms attached to the carbon atoms at positions 1,4; 1,5; 1,6; and 1,7.

A knowledge of all conformers allows the calculation of thermodynamic quantities (e.g., standard heat of formation) from the quantum chemical results by means of the appropriate formulas of statistical thermodynamics.[22] Figures 6−8 display the SEOEM standard heats of formation $\Delta H_{f,i}^{298}$ of the conformers of octane, nonane, and decane, respectively. The fractions (populations) x_i of the conformers in the gas phase, as a first approximation, can be calculated as

$$x_i = \frac{\exp(-\Delta E_i/(kT))}{\sum_j \exp(-\Delta E_j/(kT))} \tag{2}$$

where ΔE_i is the difference between the energies of conformer i and the conformer with the lowest energy (global minimum). The calculated fractions at 298.15 K are to be seen in Figures 6−8. From a knowledge of the population of each conformer and its standard heat of formation, the gas-phase standard heats of formation of unbranched aliphatic alkanes can be obtained as

$$\Delta H_f^{298} = \sum_i x_i \Delta H_{f,i}^{298} \tag{3}$$

Table 2 displays the experimental[23] and SEOEM gas-phase standard heats of formation for several unbranched aliphatic alkanes. The agreement between the two sets of values is excellent. The influence of the inclusion of "*x*" conformations on the quality of the calculated thermochemical properties will be discussed in a forthcoming paper.

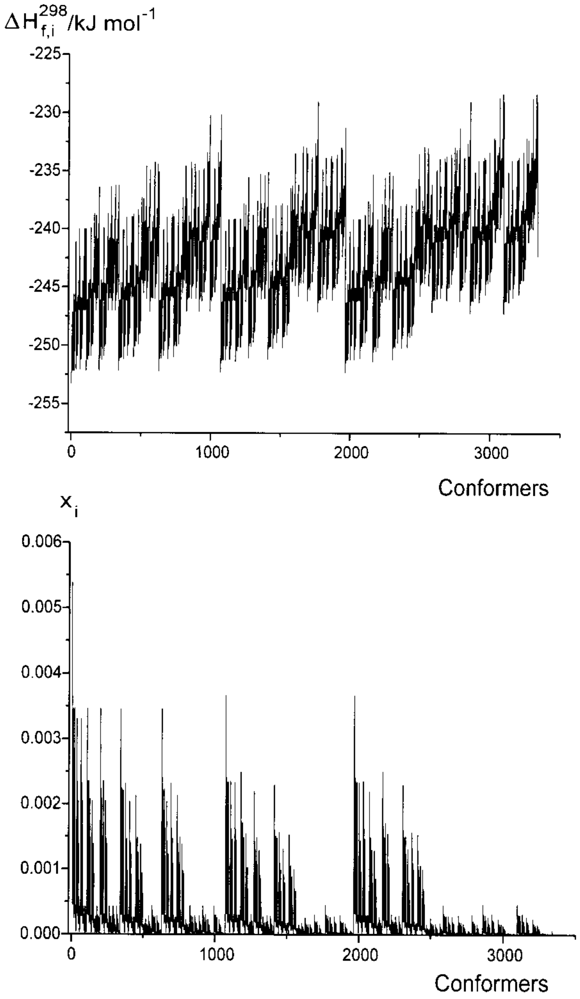

Figure 8. SEOEM standard heats of formation and populations of the conformers of decane.

TABLE 2: Experimental and Calculated Gas-Phase Standard Heats of Formation of Unbranched Aliphatic Alkanes (kJ/mol)

molecules	exptl values	calcd values
pentane	−146.9	−146.8
hexane	−167.1	−167.0
heptane	−187.7	−187.4
octane	−208.6	−207.8
nonane	−228.2	−228.2
decane	−249.5	−248.7
undecane	−270.9	−269.8

Conclusions

The SEOEM approximate quantum chemical model can be applied to study the conformational properties of large unbranched aliphatic alkanes. For the pentane, hexane, and heptane molecules, 11, 35, and 107 conformers were found, respectively. The conformational spectra for these molecules were the same at Hartree−Fock and second-order Moeller−Plesset levels too. These results allow the derivation of four rules, which can reproduce the number and sequences of the existing conformers up to undecane. The rules show that the most important factors governing the conformational behavior of unbranched aliphatic alkanes are the nonbonded repulsive−attractive (van der Waals) interactions between the hydrogen atoms attached to the carbon atoms at positions 1,4; 1,5; 1,6; and 1,7.

With the help of statistical thermodynamics, the gas-phase standard heats of formation of unbranched aliphatic alkanes can be determined from the quantum chemical calculation results. The calculated values for the C_4−C_{11} molecules closely matched the experimental values.

Acknowledgment. This work was sponsored by the Agency of Industrial Science and Technology, the Japan Science and Technology Corporation, and the New Energy and Industrial Technology Development Organization (NEDO). Gyula Tasi performed part of this work as a NEDO research fellow.

References and Notes

(1) Tasi, G.; Pálinkó, I. *Top. Curr. Chem.* **1995**, *174*, 45.

(2) Wiberg, K. B.; Murco, M. A. *J. Am. Chem. Soc.* **1988**, *110*, 8029. Frey, R. F.; Cao, M.; Newton, S. Q.; Schäfer, L. *J. Mol. Struct.: THEOCHEM* **1993**, *285*, 99. Smith, G. D.; Jaffe, R. L. *J. Phys. Chem.* **1996**, *100*, 18718. Gang, J.; Pilling, M. J.; Robertson, S. H. *J. Chem. Soc., Faraday Trans.* **1996**, *285*, 3509. Lahtela, M.; Pakkanen, T. A.; Nissfolk, F. *J. Phys. Chem. A* **1997**, *285*, 5949.

(3) Tsuzuki, S.; Schäfer, L.; Gotō, H.; Jemmis, E. D.; Hosoya, H.; Siam, K.; Tanabe, K.; Ōsawa, E. *J. Am. Chem. Soc.* **1991**, *113*, 4665.

(4) Goodman, J. M. *J. Chem. Inf. Comput. Sci.* **1997**, *37*, 876.

(5) See, for example, Dale, J. *Stereochemistry and Conformational Analysis*; Verlag Chemie: New York, 1978; pp 94−104.

(6) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

(7) Szentpály, L.; Shamovsky, I. L.; Ghosh, R.; Dakkouri, M. *J. Phys. Chem. A* **1997**, *101*, 3032.

(8) Dewar, M. J. S.; Thiel, W. J. *J. Am. Chem. Soc.* **1977**, *99*, 4899.

(9) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209.

(10) Scano, P.; Thomson, C. *J. Comput. Chem.* **1991**, *12*, 172.

(11) Tasi, G.; Mizukami, F.; Pálinkó, I. *J. Mol. Struct.: THEOCHEM* **1997**, *401*, 21. Tasi, G.; Mizukami, F.; Pálinkó, I. *Magy. Kem. Foly.* **1997**, *103*, 373. Tasi, G.; Mizukami, F. *J. Chem. Inf. Comput. Sci.* **1998**, *38*, 313.

(12) Curtiss, L. A.; Raghavachari, K.; Trucks, G. W.; Pople, J. A. *J. Chem. Phys.* **1991**, *94*, 7221.

(13) Tasi, G.; Mizukami, F. *J. Chem. Inf. Comput. Sci.* **1998**, *38*, 632.

(14) Curtiss, L. A.; Raghavachari, K.; Redfern, P. C.; Pople, J. A. *J. Chem. Phys.* **1997**, *106*, 1063.

(15) Nicolaides, A.; Rauk, A.; Glukhovtsev, M. N.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 17460.

(16) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94*, revision D.4; Gaussian, Inc.: Pittsburgh, PA, 1995.

(17) Tasi, G.; Pálinkó, I.; Halász, J.; Náray-Szabó, G. *Semiempirical Calculations on Microcomputers*; CheMicro Limited: Budapest, 1992.

(18) Tasi, G.; Mizukami, F.; Pálinkó, I. *Comput. Chem.* **1997**, *21*, 319.

(19) Stewart, J. J. P. *J. Comput.-Aided Mol. Des.* **1990**, *4*, 1.

(20) Burkert, U.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washington, DC, 1982.

(21) Gotō, H.; Ōsawa, E.; Yamato, M. *Tetrahedron* **1993**, *49*, 387.

(22) McQuarrie, D. A. *Statistical Mechanics*; Harper & Row: New York, 1976; pp 129−139.

(23) Cohen, N. *J. Phys. Chem. Ref. Data* **1996**, *25*, 1411.