MM2 Molecular Mechanics Studies of Periplanone B and Nitroxides. Empirical Methods to Evaluate the Stretching (k_s) and Bending (k_b) Force Constants of the MM2 Force Field

Kazuhisa SAKAKIBARA,* Hidetaka KAWAMURA, Takashi NAGATA, Jingzhu REN, Minoru HIROTA,
Kazuko SHIMAZAKI,† and Tastuji CHUMAN†
Department of Synthetic Chemistry, Faculty of Engineering, Yokohama National University, Hodogaya-ku, Yokohama 240
† Life Science Research Laboratory, Japan Tobacco Inc., Midori-ku, Yokohama 227

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The MM2 force field has been extended so as to deal with periplanone B and nitroxides by using empirical relationships which enable us to derive the MM2 stretching (k_s) and bending force (k_b) constants systematically. The stretching force constants (k_s) could be correlated well with the bond order (N) and equilibrium bond length (r_0) by the equation $k_s=a(N/r_0{}^3)+b$. Three different sets of parameters (a, b) were assigned to the bonds, which were classified according to the atoms forming the bonds. The bending force constants (k_b) could be estimated by the equation $k_b=A\sqrt{k_{s1}\cdot k_{s2}}+B$, where k_{s1} and k_{s2} are the stretching force constants of the bonds which comprise the bond angle. The angle types were classified into six groups in the MM2 force field. After assigning k_s and k_b, the torsional parameters (V_1, V_2, V_3) were determined so as to reproduce the ab initio conformational energies and structural data of the model compounds for the periplanone B and nitroxides. The MM2 calculations using the parameters thus obtained reproduced the experimental structures and conformational energies of periplanone B and the spin adducts of nitrone spin traps correctly.

Molecular mechanics is a very useful tool for organic chemists for studying the geometries and conformational equilibria of organic molecules in actual cpu time with high accuracy comparable to ab initio calculations. Among the currently available software of molecular mechanics, MM2[1,2] is the most popular program, and is widely used by many chemists. Though MM3,[3] which is an advanced version of MM2, has an advantage over MM2 in calculations involving thermodynamic quantities, vibrational frequencies, and crystal structures, MM2 has still been widely used due to the speed of calculations and the compactness of the program. Taking advantage of MM2, exhaustive conformational searches can be carried out smoothly by combining conformation search programs[4,5] with MM2 in practical cpu time on rather large molecules. The problem in molecular mechanics calculations is how to determine the appropriate force field parameters efficiently for the functional groups concerned when the force field parameters are not available. It is very useful if the proper MM2 force field parameters can be determined quickly in a systematic way using some physical constants which characterize the relevant bonds. In this study, we tried to find some good method to determine the MM2 stretching (k_s) and bending (k_b) force constants empirically. The usefulness of the method to determine the MM2 force constants and the accuracies of the determined k_s and k_b were checked by comparing the experimental results with MM2 calculations on periplanone B and nitrone spin adducts, which were formed by spin trapping between α-phenyl-N-t-butylnitrone (PBN) and short-lived reactive radicals.

Periplanone B ((3S, 4E, 8R, 9R, 10S)-8,9-epoxy-6-methylene-10,10-methyleneoxy-3-(1-methylethyl)-4-cyclodecen-1-one) is an extremely potent sex pheromone of the American cockroach (threshold$<10^{-13}$ g). Although the absolute configuration and the X-ray structure of periplanone B has already been reported,[6—9] it is necessary to further study the conformational equilibrium of periplanone B in order to understand why it is pheromonally so active. It is essential to know the critical structure which originates the pheromonal activity in the case of molecular design on bio-active compounds. Since periplanone B has many stable conformers, due to the flexibility of 10-membered-ring compounds having a germacrene skeleton, it is rather difficult to carry out an exhaustive conformational analysis and to find stable conformations whose geometries are responsible for pheromonal activity. A pioneering work concerning the conformation of periplanone B had already been performed by Still.[10] However, quantitative and reliable results could not be acquired due to the incompleteness of the force field parameters for the epoxy group, and due to the difficulty in generating possible conformations exhaustively.

A spin trapping[11] technique is very convenient, and is applied in various fields of chemistry to investigate the reaction mechanism involving free radicals,[12] to characterize short-lived reactive radical,[13] or to monitor and analyze radical species in the environment.[14] Since spin adducts, which are generated by a reaction between spin traps (nitrones or nitroso compounds) and short-lived free radicals, are comparatively stable nitroxides like spin label molecules,[15] characterization is usually carried out by ESR spectroscopy. However, detailed geometries and conformational equilibria of these nitroxides compounds could not be easily obtained by the experimental methods usually used for diamagnetic molecules because of the instability. Though the ab initio calculation becomes a very powerful tool for studying the geometries and conformational equilibria of rather unstable and short-lived molecules, it is not an easy task to determine the geometries and conformational energies of the spin adducts. Since the spin adducts have bulky substituents, which prevent other species from attacking the radical center, the size of molecule becomes too big to carry out ab initio calculations with reasonably big basis sets. The more accurate geometries and conformational energies that we want to have, the larger are the basis sets that we should use in the ab initio calculations. It is certain that an electron correlation will improve the accuracy and reliability of the ab initio calculations. However, these sophisticated ab initio calculations need enormous cpu times, and can not be applied to bulky spin adducts for practical purposes at present. If MM2 can deal with nitroxides properly, it would be of great help for studies using spin traps and spin labels.

In this paper, an extension of MM2 force field[1,16)] to epoxy and the nitroxide moiety is described by using empirical relationships to estimate the stretching (k_s) and bending (k_b) force constants.

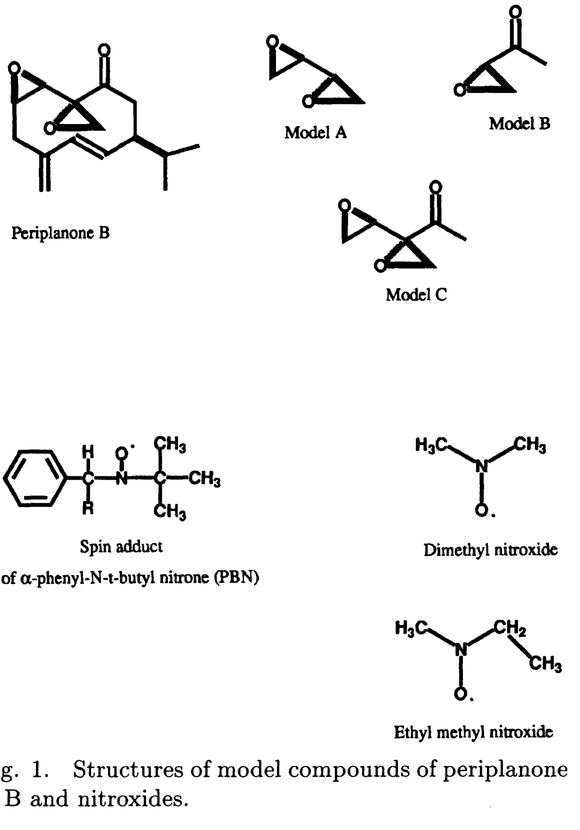
Methods

Extension of MM2 Force Field to Periplanone B and Nitroxides. Force constants and equilibrium geometry (bond lengths and bond angles) are required as force field parameters of MM2. The natural bond lengths and bond angles for the concerned functional groups are usually taken from experiments or theoretical calculations. In general, it is rather difficult to find accurate and reliable data concerning the force constants of any functional groups for which parameters have not yet been assigned. Though Allinger's guidelines[17)] for obtaining parameters are useful in several cases, they can not be easily adopted to the determination of force constants when the spectroscopic force constants are not available from the literature. It is thus necessary to find a general method by which MM2 parameters can be assigned straightforwardly. After assigning k_s and k_b, the torsional parameters (V_1, V_2, V_3) can be easily determined so as to reproduce the conformational energies of the related molecules by the least-squares method when accurate conformational energy data are available. However, it is very difficult to obtain sufficient conformational energy data from experiments. Therefore, sophisticated ab initio calculations are necessary to obtain accurate conformational energies of the concerned compounds. Since periplanone B and the spin adducts of PBN are too large to carry out ab initio full-geometry optimization, we must select model compounds for the ab initio calculations. By dividing the primary skeleton of the periplanone **B** ring, 2-oxiranyloxirane (**A**), 2-acetyloxirane (**B**), and 2-acetyl-2-oxiranyloxirane (**C**) were chosen as model molecules of periplanone B. Though Raber and his group have already reported on MM2 force field parameters of epoxides,[18)] more MM2 parameters for the structural units found in model molecules (**A**, **B**, **C**) are necessary for MM2 calculations of periplanone B. For nitroxide molecules, dimethyl nitroxide and ethyl methyl nitroxide were chosen as model compounds. Since the model compounds for nitroxides are strain free, the optimized bond lengths and bond angles obtained by ab initio calculations should indicate the true values of the natural bond lengths and bond angles. All of the model compounds are shown in Fig. 1.

A preliminary conformational search of the model molecules (**A**, **B**, **C**) was carried out by using semi-empirical molecular orbital calculations (AM1).[19)] Using these AM1 geometries as input data, ab initio geometry optimizations were carried out. As a result of ab initio calculations, model compounds **A**, **B**, and **C** were found to have 3, 2, and 4 stable conformers, respectively. For dimethyl nitroxide and ethyl methyl nitroxide, a geometry optimization was carried out for possible conformers. The optimized structures and conformational energies of model molecules **A**, **B**, **C** (6-31G*//3-21G) and ethyl methyl nitroxides (6-31G*) are shown in Table 1.[20)]

Our key idea of how to assign the stretching (k_s) and bending (k_b) force constants systematically is that k_s and k_b can be expressed as a function of the geometrical (bond length or bond angle) and/or electronic properties intrinsic to the functional groups. We therefore first checked whether our empirical methods used to estimate the stretching and bending force constants[21)] for nitrogen-containing functional groups could be applied to any other functional groups.

The natural bond lengths and bond angles of the epoxy ring were taken from the experimental data of microwave spectroscopy.[22)] Since MM2 was designed to reproduce the bond length (r_g) derived from electron diffraction, an ad hoc correction of 0.004 Å was added to the bond lengths of the experimentally derived microwave structures.[17)] The optimized bond lengths and bond angles calculated by ab initio methods for strain-free nitroxide compounds were adopted as being the natural bond lengths and bond angles for nitrox-



Periplanone B

Model A

Model B

Model C

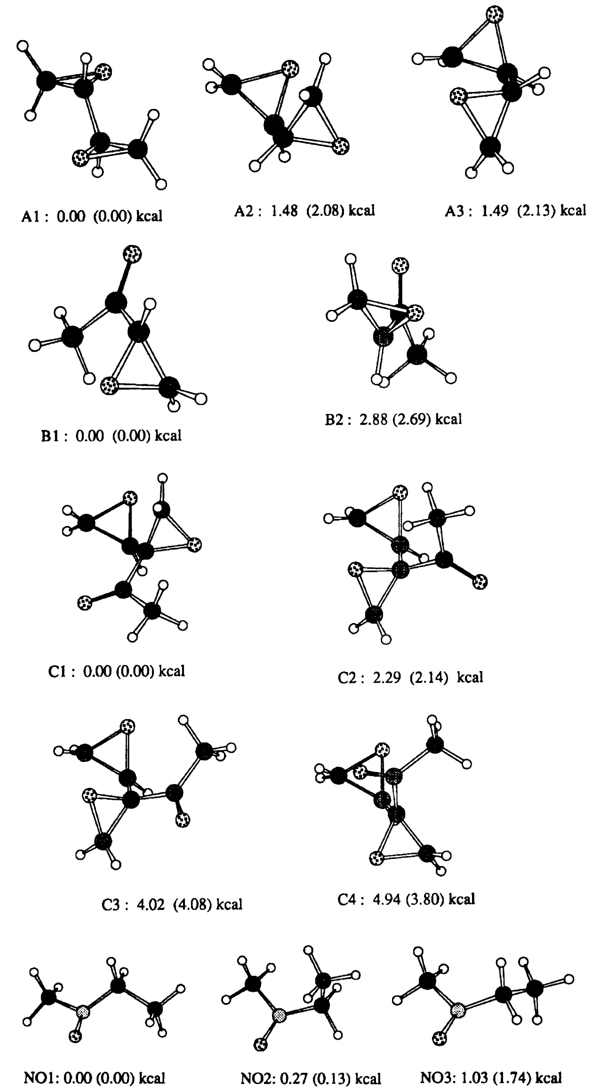
Spin adduct of α-phenyl-N-t-butyl nitrone (PBN)

Dimethyl nitroxide

Ethyl methyl nitroxide

Fig. 1. Structures of model compounds of periplanone B and nitroxides.

Table 1. The ab initio Optimized Structures and Conformational Energies of Model Molecules **A**, **B**, **C**, and Ethyl Methyl Nitroxide[a)]



a) The figures in parentheses are MM2 conformational energies.

ide molecules, because proper experimental data were not available.

The aim of this paper is to present consistent and straightforward methods for obtaining appropriate force constants (stretching, bending, or torsion parameters) of any functional groups to which the MM2 force field has not yet been assigned. The current results and various possibilities of our empirical methods to obtain stretching (k_s) and bending (k_b) force constants are discussed in turn.

Stretching Force Constants (k_s). As shown in our previous report,[21)] the stretching force constants (k_s) for bonds containing a nitrogen atom were correlated with the r_0^{-3} term, where r_0 is the equilibrium bond length,

$$k_s(r_0 - 0.690)^3 = 1.94. \tag{1}$$

This empirical equation enables us to easily calculate k_s by using an appropriate r_0. This relationship had been justified as Badger's rule[23)] for the spectroscopic force constants. By further investigating the MM2 stretching force constants in detail, an empirical relationship (k_s vs. r_0^{-3}) of this type could be applied to other type bonds. The gradients and the intercepts of empirical equations used to derive k_s were different, depending on the bond types. However, the application of this empirical method was limited because of the lack of a general guideline to select an appropriate empirical equation for the concerned bond. In order to improve this disadvantage, and to generalize an equation, we modified it by introducing the bond order (N) as another variable in addition to the equilibrium bond lengths (r_0). The modified empirical equation is

$$k_s = a(N/r_0^3) + b. \tag{2}$$

Here, N is the bond order from Paolini's bond order–bond length relationship;[24)] a and b are constants derived by a regression analysis.

In Fig. 2, a k_s vs. N/r_0^3 plot is shown. The 108 k_s data stored in the MM2(91) force field were used in this plot. This plot indicates that the all of the k_s data in the MM2 force field can correlate with N/r_0^3, though the linearity is not very good (correlation coefficient r=0.871; standard deviation σ=1.521). The regression equation is given

$$k_s = 6.638(N/r_0^3) + 1.621. \tag{2a}$$

Reviewing the plots in Fig. 2, the force constants were classified into four groups based on the bond type, and were correlated with N and r_0 in each group. The classification significantly improved the correlations. The classification of the bond type is based on the groups in the periodic table. Class A is characterized as an H–Y bond, where Y is a group IV, V, or VI element; class B has a C–Y bond, where Y is a

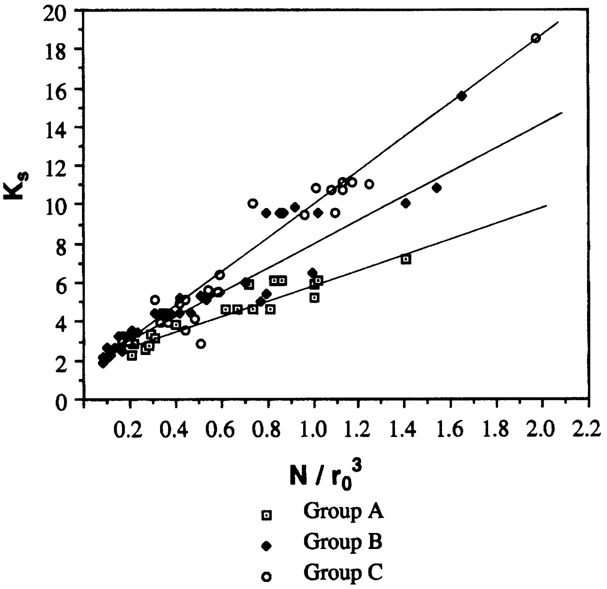


Fig. 2. The plot to derive MM2 stretching force constants (k_s) by empirical equation ($k_s = a(N/r_0^3) + b$, N: bond order calculated by Paolini's relationship, r_0: equilibrium bond length). The plot was classified into 3 groups as shown in Table 2 based on the bond types.

group IV, V, VI, or VII element; class C has an X–Y bond, where X is a group V element and Y is a group V or VI element; class D has an X–Y bond, where both X and Y are group VI elements. The regression equations for k_s are shown in Table 2. A good linear correlation was observed for the classes of A, B, and C. Since there are few k_s data available for group D in the MM2 force field, meaningful correlation could not be derived.

A process to obtain an MM2 stretching force constant (k_s) using this empirical rule is summarized as follows:

(1) Estimate an appropriate equilibrium bond length (r_0) of the relevant bond from either experiments or theoretical calculations. In the case where accurate experimental bond lengths are available, it is advisable to use them. Otherwise, the bond length from theoretical calculations of a high-level approximation can be used as a substitute.

(2) Determine the bond order (N) by Paolini's equation, as shown in

$$N = [(r_1 - r_N)/0.78 + 1]^{(1/0.33)}, \tag{3}$$

where r_1 and r_N are bond lengths with bond orders of 1 and N, respectively.

(3) Calculate k_s by putting the equilibrium bond length (r_0) and bond order (N) values into empirical Eq. 2 and using an appropriate set of parameters (a, b) from Table 2.

Bending Force Constants (k_b). For the bending constants (k_b), the situation is slightly more complicated than in the case of k_s. There have only been a few reports[25,26] that deal with the correlation between the spectroscopic bending force constants and the geometrical parameters (bond length, bond angle, etc.), nature of the chemical bond, or electronic properties. It is rather difficult to derive spectroscopic bending force constants theoretically from the structural parameters and electronic properties. Comparing the MM2 bending force constants (k_b) with the spectroscopic bending force constants, no simple correlation could be found. Allinger suggested that the spectroscopic bending force constants should be scaled to fit the MM2 force field.[17] However, the reported MM2 bending constants (k_b)[18] relevant to the epoxy ring could not be correlated with the corresponding spectroscopic force constants reported by Nakanaga.[27] It is thus necessary to develop another method to obtain the MM2 bending force constants (k_b) unequivocally. There are probably many choices in determining k_b. However, many kinds of k_b values, some of which may be improperly assigned, can predict stereochemistry fairly well because other parameters, such as the torsional ones, can be adjusted so as to compensate the effect of k_b. These situations may lead to a breakdown of the consistency of the MM2 force field. The following tentative equation, in which k_b can be correlated with the geometric mean of the stretching force constants (k_{s1} and k_{s2}) of the relevant bonds, is a one of the methods used to overcome this difficulty:

$$k_b = A\sqrt{k_{s1} \cdot k_{s2}} + B, \tag{4}$$

where k_{s1} and k_{s2} are the stretching force constants of the bonds (bond 1 and bond 2) which comprise the bond angle; A and B are empirically determined constants. In Fig. 3, a K_b vs. $\sqrt{k_{s1} \cdot k_{s2}}$ plot is shown.

By classifying the bond-angle types properly, Eq. 4 was shown to be applicable to several kinds of bond-angle types as well as the X–N–Y angle type reported earlier.[21] Though there remains some ambiguity in classifying the bond-angle type, Eq. 4 can be used to derive the bending force constants (k_b) relevant to the epoxy functional group. In Table 3, the empirical equations used to obtain the MM2 bending force constants are summarized.

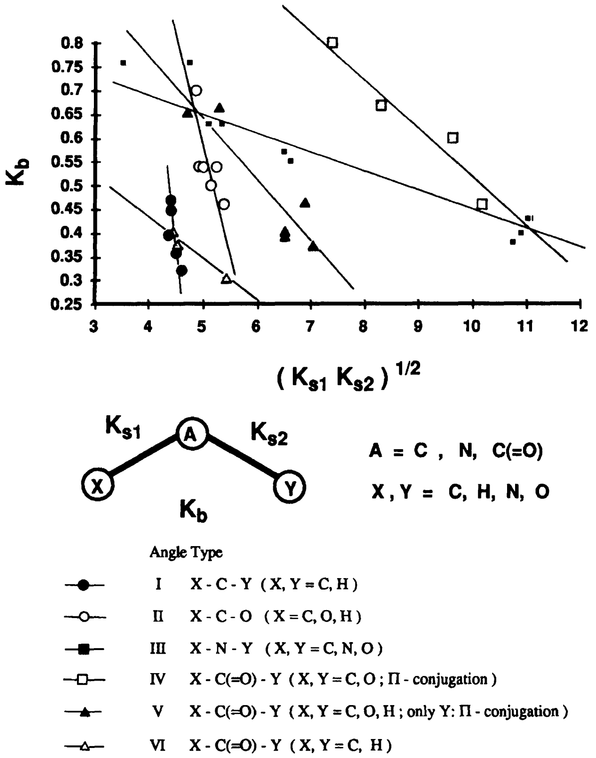


Fig. 3. The plot to derive MM3 bending force constants (k_b) by empirical equation ($k_b = A\sqrt{k_{s1} \cdot k_{s2}} + B$ (Eq. 4)).

Since only a few MM2 k_b data have been reported for the valence angles of oxygen, no empirical relation for the X–O–Y angle type could be derived from the regression analysis (Eq. 4). Therefore, the k_b value for EC–EO–EC was approximated with that given in Ref. 18, where EC and EO mean the epoxide carbon (atom type 22) and the epoxide oxygen (atom type 49), respectively. Though the k_b values for a 3-membered ring may take different values from those reported for an open chain bond when we consider the ring strain of epoxy compounds, the k_b's of EO–EC–EC (49–22–22) for 3-membered and the k_b's of O–C–C (6–1–1) for open-chain molecules were chosen to have the same value as that reported in the cyclopropane case.

Torsional Parameters (V_1, V_2, V_3). After assigning the stretching (k_s) and bending (k_b) force constants, the torsional parameters were determined so as to reproduce the geometry and conformational energy of each conformer of the model compounds (**A**, **B**, **C**, **NO**) shown in Fig. 1. Since the optimized geometries of model compounds by ab initio calculations took unusual dihedral angles for a four-atom sequence (X1–X2–X3–X4), where an epoxy oxygen or an epoxy carbon is involved (for example, H–EC–EC–EO; ca. ±110°) due to the characteristic small valence angle (ca. 60°) of the epoxy ring, it is necessary to determine the torsional parameters of the sequence of these atoms carefully so

Table 2. Parameters for the Empirical Equations to Derive Stretching Force Constants (k_s)

Class	Bond type	a	b	R	σ
A	H–X (X=IV, V, IV element)	3.82	2.08	0.956	0.437
B	X–Y (X=IV element, Y=IV, V, IV, IIV element)	7.65	1.60	0.951	1.075
C	X–Y (X=V element, Y=V, IV element)	8.75	0.950	0.968	0.790

Table 3. Equations to Derive Bending Force Constants (k_b)

$$k_b = A\sqrt{k_{s1}\cdot k_{s2}} + B$$

k_{s1}, k_{s2}: stretching force constants of bonds (bond 1 and bond 2) which comprise bond angle

Group	Angle type	A	B	R
I	X–C–Y (X, Y=C, H)	−0.789	3.921	−0.973
II	X–C–O (X=C, O, H)	−0.446	2.841	−0.891
III	X–N–Y (X, Y=C, N, O)	−0.0424	0.877	−0.957
IV	X–C(=O)–Y (X, Y=C, O)[a]	−0.109	1.599	−0.969
V	X–C(=O)–Y (X, Y=C, O, H)[b]	−0.118	1.232	−0.919
VI	X–C(=O)–Y (X, Y=C, H)[c]	−0.0887	0.782	−0.978

a) Both X and Y atoms are conjugated with carbonyl. b) Only Y atom is conjugated with carbonyl. c) Both X and Y atoms are non conjugated with carbonyl.

as to reproduce the values of the concerned dihedral angles. A general procedure for determining the torsional parameter sets is to fit the ab initio conformational energy to the MM2 conformational energy. If we assume a case in which we must determine several torsional parameter sets about the X–Y bond simultaneously, the V_1, V_2, and V_3 terms must be assigned to each torsional potential for which the torsional parameters have not been determined. If we need to obtain 4 sets of torsional parameters (A–X–Y–V, A–X–Y–U, B–X–Y–U, C–X–Y–U, for example), more than 12 (3×4) equations are necessary to determine the parameters. The simultaneous equations (Eq. 5) can be obtained from the ab initio conformational energy differences between conformers ($\Delta E_{\mathrm{ab\,initio}}$) and the corresponding MM2 conformational energy differences ($\Delta E'_{\mathrm{MM2}}$). The $\Delta E'_{\mathrm{MM2}}$'s were calculated by MM2 calculations based on the conditions that the torsional parameters to be determined were set to zero and the relevant torsional angles were fixed at the ab initio torsional angles:

$$\sum\{V_{1i}/2(1+\cos\omega_i) + V_{2i}/2(1-\cos 2\omega_i) \\ +V_{3i}/2(1+\cos 3\omega_i)\} = \Delta E_i \quad i = 1-m. \qquad (5)$$

Here, $\Delta E_i = \Delta E_{\mathrm{ab\,initio}} - \Delta E'_{\mathrm{MM2}}$, m is the number of torsional parameter sets; V_{1i}, V_{2i}, and V_{3i} are the torsional parameters to be determined; and ω_i is the torsional angle of the local minimum.

The more accurate conformational energy data concerning the torsion potential energy curves that we obtain, the more accurate and more reliable set of torsional parameters that can be obtained by solving the simultaneous equations with the least-squares method. At present, an ab initio calculation with the sophisticated large basis sets seems to be the most proper method. In our study, Hartree–Fock calculations with 6-31G* basis sets were employed because of a restriction on the available cpu time and hardware. The essential point in determining the torsional parameters is to collect a large amount of accurate conformational energy data concerning the relevant torsional potentials, as much as possible. When sufficient conformational energy data are available, the reliable torsional parameters can surely be derived by solving the simultaneous equations. If the determined torsional parameters can not reproduce the experimental results, it is necessary to reexamine whether the newly assigned stretching (k_s) and bending (k_b) force constants are proper or the experimental results are correct.

Results and Discussion

Determined MM2 Force Field Parameters for Periplanone B and Nitroxides. The thus-determined stretching (k_s), bending (k_b), and torsional (V_1, V_2, V_3) constants are given in Table 4. The atom-type numbers for the epoxy oxygen (EO), epoxy carbon (EC), nitroxide oxygen, and nitroxide nitrogen were assigned as 49, 22, 110, and 8, respectively. In order to reproduce the conformational energies and geometries of stable conformers of nitroxides determined by ab initio calculations, three long-pair atoms (atom type 20) must be located on the nitroxide oxygen (atom type 110). Though we temporarily used atom 8, which is assigned to the sp^3 nitrogen in the MM2 force field, to the nitroxide nitrogen, it may be a better method to assign a new atom type. However, this method takes a much longer time to obtain the MM2 force field parameters. Since the reasonable conformational energies and geometries could be obtained for nitroxides, as shown below, by our method, a new atom type for the nitroxide nitrogen was not assigned.

MM2 Calculations on the Model Compounds

Table 4. MM2 Parameters for Periplanone B and Nitroxides

Parameters for Periplanone B

1. Stretching parameters

Bond type[b)]	k_s/mdyn Å^{-1}	l_0/Å	Moment/D
5–22	4.90	1.086	0.0
49–22	4.95	1.440	−0.735
22–22	4.66	1.476	0.0
3–22	4.35	1.495	0.3

2. Bending parameters

Angle type[b)]	k_b/mdyn Å^{-1} rad^{-2}	Θ_0/deg
5–22–49	0.643	114.20
5–22–22	0.150	119.50
20–49–20	0.240	131.00
20–49–22	0.350	103.00
49–22–22	0.698	113.46
49–22–22[a)]	0.698	59.17
22–49–22[a)]	0.620	61.67
3–22–49	0.758	115.15
3–22–22	0.347	118.89
1–3–22	0.394	115.39

3. Torsional parameters

Dihedral angle type[b)]	V_1	V_2	V_3
49–22–22–49	1.2	0.1	0.6
49–22–22–22	−0.28	−0.24	−0.28
22–49–22–22	0.2	0.3	0.4
49–22–3–7	−0.36	1.08	−0.36
49–22–22–3	0.5	−0.9	−0.2
22–49–22–3	0.25	−0.5	−0.25
1–3–22–22	0.6	1.125	0.75
1–3–22–49	0.9	1.784	0.2
22–3–1–5	−0.2	0.1	1.0
1–3–22–5	1.7	−0.2	−0.5
3–22–22–22	−0.2	−1.0	0.1
7–3–22–22	−0.13	0.904	0.05
22–3–1–1	0.55	−0.18	0.4
1–22–22–49	0.0	0.0	0.53
1–22–49–22	0.0	0.0	1.21
2–1–22–49	0.0	0.0	0.53
49–22–1–5	0.0	0.0	0.53

Parameters for Nitroxides

1. Stretching parameters

Bond type[c)]	k_s/mdyn Å^{-1}	l_0/Å	Moment/D
8–110	9.49	1.278	2.12
1–8	4.94	1.447	0.04

2. Bending parameters

Angle type[c)]	k_b/mdyn Å^{-1} rad^{-2}	Θ_0/deg
1–8–110	0.575	115.30
1–8–1	0.650	117.65
5–1–8	0.654	109.78
20–8–110	0.240	100.90
20–110–8	0.240	110.61
1–8–20	0.500	101.83
20–110–20	0.240	108.30

3. Torsional parameters

Dihedral angle type[c)]	V_1	V_2	V_3
5–1–8–110	0.0	0.0	0.109
5–1–8–1	0.0	0.0	0.900
20–110–8–20	0.0	0.0	0.0
1–1–8–110	−0.808	−0.668	0.551
2–1–8–110	−0.808	−0.668	0.551
1–1–8–1	2.023	−1.169	0.775
2–1–8–1	2.023	−1.169	0.775

a) 3-membered ring. b) Atom type: 49-epoxide oxygen, 22-epoxide carbon. c) Atom type: 110-nitroxide oxygen.

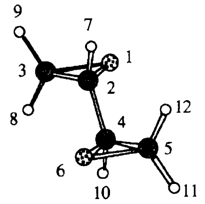
of Periplanone B. MM2 calculations using the thus-determined parameters could accurately reproduce the conformational equilibria determined by ab initio calculations of the model compounds of periplanone B (**A**, **B**, **C**) in very short cpu times. The results are given in Table 1. The geometry of the global minimum of each model compound is given in Table 5. The geometries of the other conformers were also calculated with as good an accuracy as that of the global minimum. The bond lengths were calculated within an error of 0.02 Å with reference to those from ab initio calculations. The largest discrepancy between the ab initio and MM2 calculations regarding the bond angles was 3°. Though the maximum disagreement of the dihedral angles between ab initio and MM2 is rather large (<6°), compared with the discrepancies in the bond lengths and bond angles, the relative orientation of the epoxy ring and the carbonyl moiety was properly reproduced. Since the parameters set seemed to be both accurate and reliable, we next carried out an exhaustive conformational analysis of periplanone B and its analogues. The MM2 calculations have shown that these biological active molecules have a common ten-membered ring structure superimposable on that of the X-ray structure of periplanone B.[28)] The pheromonal activity could be correlated well with the characteristic skeletal ring conformation and arrangements of the epoxy rings, carbonyl group, and diene moiety in these molecules.

MM2 Calculations on Nitroxides. MM2 calculations with the thus-determined force field parameters

Table 5. Geometries of Model Molecules[a)]

Model A (The most stable conformer)

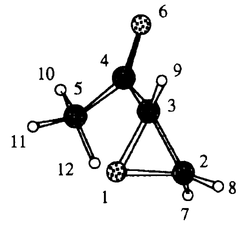
Bond (Å)	*a*	*b*	*a*−*b*	Bond	*a*	*b*	*a*−*b*
O(1)–C(2)	1.4682	1.4439	0.0243	O(1)–C(3)	1.4749	1.4448	0.0301
C(2)–C(3)	1.4717	1.4835	−0.0118	C(2)–C(4)	1.4749	1.4909	−0.0160
C(2)–H(7)	1.0713	1.0894	−0.0181	C(3)–H(8)	1.0712	1.0878	−0.0166
C(3)–H(9)	1.0705	1.0881	−0.0176	C(4)–C(5)	1.4715	1.4835	−0.0120
C(4)–O(6)	1.4683	1.4439	0.0244	C(4)–H(10)	1.0713	1.0895	−0.0182
C(5)–O(6)	1.4750	1.4448	0.0302	C(5)–H(11)	1.0705	1.0881	−0.0176
C(5)–H(12)	1.0712	1.0878	−0.0166				



Atoms	*a*	*b*	*a*−*b*	Atoms	*a*	*b*	*a*−*b*
C(2)–O(1)–C(3)	60.005	61.800	−1.795	O(1)–C(2)–C(3)	60.225	59.12	1.097
O(1)–C(2)–C(4)	113.456	113.708	−0.252	O(1)–C(2)–H(7)	115.368	113.825	1.543
C(3)–C(2)–C(4)	119.994	120.409	−0.415	C(3)–C(2)–H(7)	119.139	118.006	1.133
C(4)–C(2)–H(7)	115.974	117.424	−1.450	O(1)–C(3)–C(2)	59.770	59.072	0.698
O(1)–C(3)–H(8)	114.752	114.297	0.455	O(1)–C(3)–H(9)	114.651	114.199	0.452
C(2)–C(3)–H(8)	119.250	119.112	0.138	C(2)–C(3)–H(9)	119.210	118.376	0.834
H(8)–C(3)–H(9)	116.347	117.697	−1.350	C(2)–C(4)–C(5)	119.974	120.403	−0.429
C(2)–C(4)–O(6)	113.420	113.723	−0.303	C(2)–C(4)–H(10)	116.005	117.423	−1.418
C(5)–C(4)–O(6)	60.230	59.128	1.102	C(5)–C(4)–H(10)	119.144	118.005	1.139
O(6)–C(4)–H(10)	115.355	113.823	1.532	C(4)–C(5)–O(6)	59.778	59.069	0.709
C(4)–C(5)–H(11)	119.202	118.368	0.834	C(4)–C(5)–H(12)	119.267	119.135	0.132
O(6)–C(5)–H(11)	114.641	114.198	0.443	O(6)–C(5)–H(12)	114.760	114.294	0.466
H(11)–C(5)–H(12)	116.338	117.689	−1.351	C(4)–O(6)–C(5)	59.992	61.803	−1.811
O(1)–C(2)–C(3)–H(8)	−103.242	−102.438	−0.804	O(1)–C(2)–C(3)–H(9)	103.136	102.677	0.459
O(1)–C(2)–C(4)–C(5)	−112.068	−113.519	1.451	O(1)–C(2)–C(4)–O(6)	179.948	179.559	0.389
O(1)–C(2)–C(4)–H(10)	43.012	43.085	−0.073	O(1)–C(3)–C(2)–C(4)	101.493	101.087	0.406
O(1)–C(3)–C(2)–H(7)	−104.251	−102.421	−1.830	C(2)–O(1)–C(3)–H(8)	110.737	110.597	0.140
C(2)–O(1)–C(3)–H(9)	−110.735	−109.765	−0.970	C(2)–C(4)–C(5)–O(6)	−101.461	−101.110	−0.351
C(2)–C(4)–C(5)–H(11)	155.409	156.211	−0.802	C(2)–C(4)–C(5)–H(12)	1.787	1.312	0.475
C(2)–C(4)–O(6)–C(5)	112.301	112.415	−0.114	C(3)–O(1)–C(2)–C(4)	−112.307	−112.430	0.123
C(3)–O(1)–C(2)–H(7)	110.461	109.515	0.946	C(3)–C(2)–C(4)–C(5)	179.931	179.565	0.366
C(3)–C(2)–C(4)–O(6)	111.944	112.643	−0.699	C(3)–C(2)–C(4)–H(10)	−24.989	−23.831	−1.158
C(4)–C(2)–C(3)–H(8)	−1.749	−1.351	−0.398	C(4)–C(2)–C(3)–H(9)	−155.370	−156.236	0.866
C(4)–O(6)–C(5)–H(11)	110.732	109.754	0.978	C(4)–O(6)–C(5)–H(12)	−110.756	−110.625	−0.131
C(5)–C(4)–C(2)–H(7)	24.892	22.941	1.951	C(5)–O(6)–C(4)–H(10)	−110.475	−109.515	−0.960
O(6)–C(4)–C(2)–H(7)	−43.095	−43.981	0.886	O(6)–C(4)–C(5)–H(11)	−103.130	−102.679	−0.451
O(6)–C(4)–C(5)–H(12)	103.248	102.422	0.826	O(6)–C(5)–C(4)–H(10)	104.235	102.419	1.816
H(7)–C(2)–C(3)–H(8)	152.507	155.141	−2.634	H(7)–C(2)–C(3)–H(9)	−1.114	0.256	−1.370
H(7)–C(2)–C(4)–H(10)	179.966	179.545	0.421	H(10)–C(4)–C(5)–H(11)	1.104	−0.259	1.363
H(10)–C(4)–C(5)–H(12)	−152.518	−155.159	2.641				

Model B (The most stable conformer)

Bond (Å)	*a*	*b*	*a*−*b*	Bond	*a*	*b*	*a*−*b*
O(1)–C(2)	1.4677	1.4440	0.0237	O(1)–C(3)	1.4614	1.4447	0.0167
C(2)–C(3)	1.4800	1.4874	−0.0074	C(2)–H(7)	1.0704	1.0877	−0.0173
C(2)–H(8)	1.0701	1.0882	−0.0181	C(3)–C(4)	1.4928	1.5139	−0.0211
C(3)–H(9)	1.0702	1.0892	−0.0190	C(4)–C(5)	1.5063	1.5167	−0.0102
C(4)–O(6)	1.2110	1.2104	0.0006	C(5)–H(10)	1.0797	1.1139	−0.0342
C(5)–H(11)	1.0830	1.1136	−0.0306	C(5)–H(12)	1.0828	1.1133	−0.0305

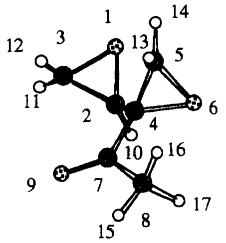


Atoms	*a*	*b*	*a*−*b*	Atoms	*a*	*b*	*a*−*b*
C(2)–O(1)–C(3)	60.697	61.982	−1.2850	O(1)–C(2)–C(3)	59.443	59.033	0.4100
O(1)–C(2)–H(7)	114.888	114.269	0.6190	O(1)–C(2)–H(8)	114.924	114.152	0.7720
C(3)–C(2)–H(7)	119.489	119.313	0.1760	C(3)–C(2)–H(8)	118.772	118.592	0.1800
H(7)–C(2)–H(8)	116.406	117.440	−1.0340	O(1)–C(3)–C(2)	59.860	58.985	0.8750
O(1)–C(3)–C(4)	115.149	117.479	−2.3300	O(1)–C(3)–H(9)	116.088	113.645	2.4430
C(2)–C(3)–C(4)	118.885	118.504	0.3810	C(2)–C(3)–H(9)	118.754	114.895	3.8590
C(4)–C(3)–H(9)	116.001	119.151	−3.1500	C(3)–C(4)–C(5)	115.509	118.956	−3.4470
C(3)–C(4)–O(6)	120.175	119.479	0.6960	C(5)–C(4)–O(6)	124.306	121.559	2.7470
C(4)–C(5)–H(10)	109.353	111.196	−1.8430	C(4)–C(5)–H(11)	109.261	110.002	−0.7410
C(4)–C(5)–H(12)	111.417	110.572	0.8450	H(10)–C(5)–H(11)	110.086	108.378	1.7080
H(10)–C(5)–H(12)	109.633	108.286	1.3470	H(11)–C(5)–H(12)	107.064	108.323	−1.2590
O(1)–C(2)–C(3)–C(4)	−103.941	−106.629	2.688	O(1)–C(2)–C(3)–H(9)	105.155	103.704	1.451
O(1)–C(3)–C(2)–H(7)	103.154	102.287	0.867	O(1)–C(3)–C(2)–H(8)	−103.539	−102.497	−1.042
O(1)–C(3)–C(4)–C(5)	−7.861	−3.691	−4.170	O(1)–C(3)–C(4)–O(6)	171.001	175.451	−4.450
C(2)–O(1)–C(3)–C(4)	110.150	108.357	1.793	C(2)–O(1)–C(3)–H(9)	−109.576	−105.841	−3.735
C(2)–C(3)–C(4)–C(5)	60.145	64.070	−3.925	C(2)–C(3)–C(4)–O(6)	−120.993	−116.787	−4.206
C(3)–O(1)–C(2)–H(7)	−110.872	−110.840	−0.032	C(3)–O(1)–C(2)–H(8)	109.999	110.034	−0.035
C(3)–C(4)–C(5)–H(10)	−178.088	179.222	2.690	C(3)–C(4)–C(5)–H(11)	61.361	59.154	2.207
C(3)–C(4)–C(5)–H(12)	−56.735	−60.447	3.712	C(4)–C(3)–C(2)–H(7)	−0.787	−4.343	3.556
C(4)–C(3)–C(2)–H(8)	152.520	150.874	1.646	C(5)–C(4)–C(3)–H(9)	−148.170	−147.567	−0.603
C(6)–C(4)–C(3)–H(9)	30.692	31.576	−0.884	O(6)–C(4)–C(5)–H(10)	3.103	0.097	3.006
O(6)–C(4)–C(5)–H(11)	−117.448	−119.969	2.521	O(6)–C(4)–C(5)–H(12)	124.456	120.429	4.027
H(7)–C(2)–C(3)–H(9)	−151.691	−154.010	2.319	H(8)–C(2)–C(3)–H(9)	1.616	1.207	0.409

Table 5. (Continued)

Model C (The most stable conformer)

Bond (Å)	*a*	*b*	*a*−*b*	Bond	*a*	*b*	*a*−*b*
O(1)–C(2)	1.4661	1.4438	0.0223	O(1)–C(3)	1.4777	1.4427	0.0350
C(2)–C(3)	1.4653	1.4849	−0.0196	C(2)–C(4)	1.4809	1.4958	−0.0149
C(2)–H(10)	1.0705	1.0889	−0.0184	C(3)–H(11)	1.0698	1.0880	−0.0182
C(3)–H(12)	1.0695	1.0880	−0.0185	C(4)–C(5)	1.4772	1.4891	−0.0119
C(4)–O(6)	1.4604	1.4448	0.0156	C(4)–C(7)	1.4965	1.5179	−0.0214
C(5)–O(6)	1.4724	1.4431	0.0293	C(5)–H(13)	1.0701	1.0871	−0.0170
C(5)–H(14)	1.0678	1.0868	−0.0190	C(7)–C(8)	1.5046	1.5166	−0.0120
C(7)–O(9)	1.2120	1.2104	0.0016	C(8)–H(15)	1.0798	1.1139	−0.0341
C(8)–H(16)	1.0827	1.1129	−0.0302	C(8)–H(17)	1.0829	1.1135	−0.0306



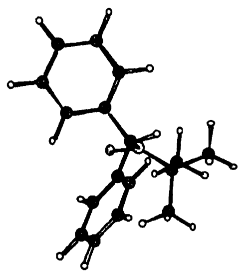
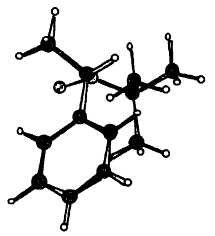
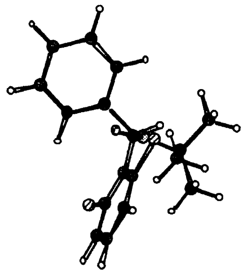
Atoms	*a*	*b*	*a*−*b*	Atoms	*a*	*b*	*a*−*b*
C(2)–O(1)–C(3)	59.705	61.919	−2.214	O(1)–C(2)–C(3)	60.541	59.005	1.536
O(1)–C(2)–C(4)	114.972	116.448	−1.476	O(1)–C(2)–H(10)	114.703	114.909	−0.206
C(3)–C(2)–C(4)	117.962	119.680	−1.718	C(3)–C(2)–H(10)	119.781	117.847	1.934
C(4)–C(2)–H(10)	116.475	116.306	0.169	O(1)–C(3)–C(2)	59.754	59.072	0.678
O(1)–C(3)–H(11)	114.815	114.197	0.618	O(1)–C(3)–H(12)	114.691	114.272	0.419
C(2)–C(3)–H(11)	118.745	118.785	−0.040	C(2)–C(3)–H(12)	119.504	118.510	0.994
H(11)–C(3)–H(12)	116.457	117.848	−1.391	C(2)–C(4)–C(5)	118.466	121.067	−2.601
C(2)–C(4)–O(6)	116.706	113.701	3.005	C(2)–C(4)–C(7)	115.804	114.959	0.845
C(5)–C(4)–O(6)	60.158	58.904	1.254	C(5)–C(4)–C(7)	119.315	118.695	0.620
O(6)–C(4)–C(7)	114.532	117.321	−2.789	C(4)–C(5)–O(6)	59.355	59.016	0.339
C(4)–C(5)–H(13)	119.855	118.398	1.457	C(4)–C(5)–H(14)	116.686	121.486	−4.800
O(6)–C(5)–H(13)	114.604	114.202	0.402	O(6)–C(5)–H(14)	114.454	113.774	0.680
H(13)–C(5)–H(14)	118.023	116.165	1.858	C(4)–O(6)–C(5)	60.487	62.080	−1.593
C(4)–C(7)–C(8)	115.836	119.493	−3.657	C(4)–C(7)–O(9)	120.000	119.127	0.873
C(8)–C(7)–O(9)	124.150	121.318	2.832	C(7)–C(8)–H(15)	109.296	111.123	−1.827
C(7)–C(8)–H(16)	111.406	110.817	0.589	C(7)–C(8)–H(17)	109.326	110.070	−0.744
H(15)–C(8)–H(16)	109.617	108.167	1.450	H(15)–C(8)–H(17)	110.123	108.248	1.875
H(16)–C(8)–H(17)	107.049	108.323	−1.274				
O(1)–C(2)–C(3)–H(11)	−103.550	−102.476	−1.074	O(1)–C(2)–C(3)–H(12)	103.041	102.705	0.336
O(1)–C(2)–C(4)–C(5)	−3.667	−7.211	3.544	O(1)–C(2)–C(4)–O(6)	−72.513	−74.006	1.493
O(1)–C(2)–C(4)–C(7)	148.069	146.775	1.294	O(1)–C(3)–C(2)–C(4)	104.424	104.812	−0.388
O(1)–C(3)–C(2)–H(10)	−103.284	−103.788	0.504	C(2)–O(1)–C(3)–H(11)	110.103	110.255	−0.152
C(2)–O(1)–C(3)–H(12)	−111.062	−109.890	−1.172	C(2)–C(4)–C(5)–O(6)	−106.160	−100.642	−5.518
C(2)–C(4)–C(5)–H(13)	151.253	156.711	−5.458	C(2)–C(4)–C(5)–H(14)	−2.231	−0.059	−2.172
C(2)–C(4)–O(6)–C(5)	109.058	113.164	−4.106	C(2)–C(4)–C(7)–C(8)	150.605	149.950	0.655
C(2)–C(4)–C(7)–O(9)	−28.085	−27.221	−0.864	C(3)–O(1)–C(2)–C(4)	−109.330	−110.263	0.933
C(3)–O(1)–C(2)–H(10)	111.597	108.775	2.822	C(3)–C(2)–C(4)–C(5)	−72.137	−74.970	2.833
C(3)–C(2)–C(4)–O(6)	−140.983	−141.765	0.782	C(3)–C(2)–C(4)–C(7)	79.598	79.016	0.582
C(4)–C(2)–C(3)–H(11)	0.874	2.336	−1.462	C(4)–C(2)–C(3)–H(12)	−152.535	−152.483	−0.052
C(4)–O(6)–C(5)–H(13)	111.413	109.774	1.639	C(4)–O(6)–C(5)–H(14)	−107.699	−113.652	5.953
C(4)–C(7)–C(8)–H(15)	177.838	−178.829	−3.333	C(4)–C(7)–C(8)–H(16)	56.552	60.875	−4.323
C(4)–C(7)–C(8)–H(17)	−61.561	−58.926	−2.635	C(5)–C(4)–C(2)–H(10)	134.660	133.203	1.457
C(5)–C(4)–C(7)–C(8)	−57.913	−55.409	−2.504	C(5)–C(4)–C(7)–O(9)	123.398	127.421	−4.023
C(5)–O(6)–C(4)–C(7)	−111.016	−108.635	−2.381	O(6)–C(4)–C(2)–H(10)	65.815	66.408	−0.593
O(6)–C(4)–C(5)–H(13)	−102.587	−102.648	0.061	O(6)–C(4)–C(5)–H(14)	103.930	100.582	3.348
O(6)–C(4)–C(7)–C(8)	10.307	12.262	−1.955	O(6)–C(4)–C(7)–O(9)	−168.383	−164.909	−3.474
O(6)–C(5)–C(4)–C(7)	103.111	106.314	−3.203	C(7)–C(4)–C(2)–H(10)	−73.604	−72.811	−0.793
C(7)–C(4)–C(5)–H(13)	0.524	3.666	−3.142	C(7)–C(4)–C(5)–H(14)	−152.960	−153.105	0.145
O(9)–C(7)–C(8)–H(15)	−3.534	−1.722	−1.812	O(9)–C(7)–C(8)–H(16)	−124.819	−122.018	−2.801
O(9)–C(7)–C(8)–H(17)	117.068	118.181	−1.113	H(10)–C(2)–C(3)–H(11)	153.167	153.737	−0.570
H(10)–C(2)–C(3)–H(12)	−0.242	−1.083	0.841				

a) *a*: ab initio calculations, *b*: MM2 calculations.

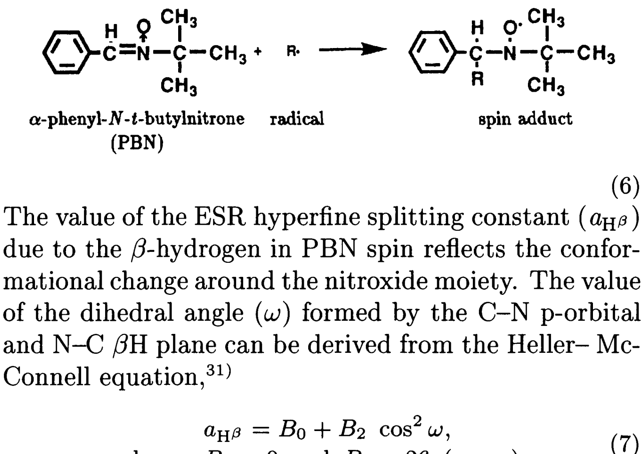
for the nitroxide function could well reproduce the ab initio geometries of the strain free molecules, such as the dimethyl and ethyl methyl nitroxides. The natural bond length for N–O (1.28 Å) and the bond angle for C–N–O (117°), as well as the conformational energies of ethyl methyl nitroxide (Table 1) were accurately calculated by MM2. Next, the reliability of the determined MM2 force field parameters for nitroxide were checked by comparing the calculated MM2 structures with those from experiments, because the actual stable nitroxides have distorted or strained structures around the nitroxide moiety due to the neighboring bulky substituents. A longer N–O bond and larger C–N–O and C–N–C bond angles than those of the strain free nitroxides are characteristic structural features of stable nitroxides. Since the X-ray structures of di-*t*-butyl nitroxide[29)] and 4-oxo-2,2,6,6-tetramethyl-1-piperidinyloxyl,[30)] which are typical stable nitroxides (known as spin label molecules), were available, the MM2 calculations were carried out on both molecules. The structures of heavy atoms, except for hydrogens, in such bulky nitroxides, were well calculated by MM2 (the positions of the hydrogen atoms were not shown in the X-ray structures). The unusually large bond angles (C–N–O: 115—118°, C–N–C: 120—130°) for the sp^3 nitrogen atom and an intermediate bond length (N–O: 1.28—1.30 Å) between the single (N–O: 1.43 Å) and double (N=O: 1.16 Å) bond were correctly reproduced by MM2 calculations.

It is not certain whether the positions of the hydrogen atoms in stable nitroxides can be calculated well in

Table 6. Structures of PBN Spin Adducts Determined By ESR and MM2

			
MM2 Calculation	R=phenyl	R=methyl	R=2,6-dichlorophenyl
N–O	1.2931 Å	1.2928 Å	1.2936 Å
N–C	1.4770 Å	1.4761 Å	1.4762 Å
	1.4800 Å	1.4808 Å	1.4797 Å
C–N–O	115.53 °	115.22 °	118.27 °
	115.87 °	114.91 °	119.26 °
C–N–C	121.63 °	121.40 °	121.70 °
ω	76.1 °	74.4 °	60.2 °
ESR Experiment			
ω (exptl. by ESR)	74.0 °	68.1 °	57.8 °
$a_{H\beta}$ (gauss)	1.99	3.63	7.39

MM2, because reliable experimental structures of the conformation of the hydrogen atoms were not available in the X-ray experiments.[29,30] Therefore, the experimental structures determined by ESR of several PBN spin adducts were compared with the MM2-calculated structures.



(6)

The value of the ESR hyperfine splitting constant ($a_{H\beta}$) due to the β-hydrogen in PBN spin reflects the conformational change around the nitroxide moiety. The value of the dihedral angle (ω) formed by the C–N p-orbital and N–C βH plane can be derived from the Heller- McConnell equation,[31)]

$$a_{H\beta} = B_0 + B_2 \cos^2\omega, \quad \text{where} \quad B_0 = 0 \text{ and } B_2 = 26 \text{ (gauss)}. \tag{7}$$

Janzen's group has reported the conformations of nitroxides (spin adducts) which were formed by the reaction of PBN with alkyl radicals from the ENDOR spectra.[32)] They discussed that the $a_{H\beta}$ value became larger when the bulky radicals were trapped by PBN, due to a steric repulsion between the substituents in the spin adducts. The dihedral angle (ω) formed by the C–N p-orbital and the N–C βH plane takes a smaller value as the $a_{H\beta}$ value becomes larger. It is interesting to see how well the MM2 can calculate the structures of the PBN spin adducts. We carried out MM2 calculations on the phenyl, methyl, and 2,6-dichlorophenyl radical spin adducts of PBN, because the magnitude in the change of the $a_{H\beta}$ values (phenyl: 1.99 gauss,[32)] methyl: 3.63,[32)] 2,6-dichlorophenyl: 7.39 gauss[33)]) are big and the change in the conformation can be easily detected. The MM2-calculated and experimental values of the dihedral angles are given in Table 6. MM2 can calculate the conformation of the β-hydrogen shown in ESR experiments well in a shorter cpu time than that by molecular orbital calculations. Though semi-empirical molecular orbital calculations (AM1 or PM3 for example) can be carried out on these PBN spin adducts by using much longer running times of the computations, the accuracy of these MO calculations on the molecular structures was rather poor. The N–O bond length was calculated to be ca. 1.22 Å, which is too small for N–O. It was very difficult to reproduce the correct N–O bond length (ca. 1.28 Å) in the MO calculations. Even with ab initio calculations with a split valence basis set, it failed to predict the correct N–O bond length. Split-valece+polarization or even larger basis set can be used to calculate the structures of the nitroxides correctly in the Hartree–Fock ab initio method. However, the ab initio calculations with this level of accuracy require an enormous amounts of running cpu time, which is not practical for experimental chemists. Considering the accuracy of the calculations and the required cpu times, molecular mechanics is the most appropriate method to obtain accurate geometries and conformational energies of nitroxides for actual purposes.

Conclusion

At least in principle, our method can generally be applied to estimations of the MM2 parameters necessary to calculate a heteroatom-containing system. The thus-determined MM2 force field parameters could predict the geometries and conformational energies with an accuracy equal to the experimental methods. The process used to estimate the stretching and bending force constants is very simple and unequivocal. The evaluation of the torsional parameters can be performed smoothly by fitting the ab initio conformational energies to the MM2 conformational energies when the stretching and bending parameters have been properly assigned. In addition to the quickness in determining of the missing force field parameters, this method is consistent and it is not probable that new parameters thus determined may lead to a breakdown of the consistency of the MM2 force field. In this way, whoever wants to know the structures and conformational energies for any molecules can easily obtain this information by MM2 with sufficient accuracy for most purposes. At present, however, the process used to estimate the bending force constants is not complete, and needs some improvement.

Methods of Calculations

Molecular mechanics calculations were performed by using the MM2(91) program with SUN SPARC station IPC. Ab initio calculations were carried out by the Hartree–Fock method with a Gaussian 86 program[34)] on a HITAC M-680H at the Institute for Molecular Science (IMS) or on a FACOM M-780 at the National Chemical Laboratory for Industry. Before the geometry optimization with ab initio calculation, the probable stable conformations were presearched by semi-empirical molecular orbital calculations (AM1 and PM3) and the obtained geometries were used as input data for ab initio calculations.

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