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Empirical Force Field Study of Geometries and Conformational Transitions of Some Organic Molecules

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Abstract: Minimum energy geometries and conformational energy differences of two classes of organic molecules—saturated hydrocarbons and molecules with methyl groups adjacent to double bonds—are investigated in detail by using a molecular mechanics force field of the type commonly employed for macromolecules. The potential energy function is parameterized to reproduce relevant properties of the simpler molecules and is transferred to more complicated compounds. Although the form of the potential function is simpler than those most frequently employed in small molecule calculations, the properties examined are determined with comparable accuracy; of particular interest is that single torsional terms can be used to achieve good agreement with experiment for relative barrier values in molecules like butane. The relationship between torsional, van der Waals, and electrostatic effects within molecules is investigated. The calculations on the molecules containing methyl groups adjacent to double bonds, including carbon–carbon and carbon–oxygen double bonds, test whether the force field can accurately represent widely varying rotational barriers in a class of similar molecules. Detailed calculations are reported for the butane rotational potential, cyclohexane ring inversion, and the geometry of the overcrowded molecule tri-*tert*-butylmethane.

1. Introduction

The computation of potential energy changes in chemical systems is of general interest. Within the Born–Oppenheimer approximation, this requires the calculation of the change in potential energy of a molecule as a function of changes in its nuclear coordinates. Molecular mechanics calculations[1-3] are widely used for this purpose in the study of systems ranging from small molecules to liquids and macromolecules. The force fields used in such calculations consist of a functional form for the potential energy that has a minimum number of associated parameters and is transferable from one molecule to another. The individual energy contributions preferably represent simply interpretable and physically plausible interactions. They are commonly comprised of bonding terms, which express the energy as a function of the deviation from preferred bond lengths, bond angles, and torsional angles, and nonbonding terms, which represent interactions such as van der Waals and electrostatic forces.

As part of a continuing program to obtain an improved force field for the study of macromolecules of biological interest,[4] we have investigated molecules belonging to two series, the alkanes and molecules with methyl groups bonded to sp^2 carbons. We focus primarily on minimum energy geometries and the potential energy changes as a function of conformation. In doing so, force field parameters are developed that should be useful for organic and macromolecular simulations.

The molecules studied are basic to organic chemistry and to biological macromolecules. The availability of accurate data was a criterion for selecting a particular molecule for study. Such data are derived from experimental measurements and ab initio

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quantum mechanical calculations. The latter, if done with a large enough basis set and appropriate correlation corrections, can provide reliable information not available from experiment.

This analysis stresses the parts of the potential energy function most influential in determining minimum energy geometries and conformational transitions, namely, the nonbonded terms, torsional force constants (intrinsic barrier heights), and reference values for the internal terms (the parameters that specify preferred bond lengths, angles, and torsional angles). The bond length and angle reference parameters strongly influence the calculated minimum energy geometries and as such also affect the nonbonded interactions. The bond length and angle force constants are not treated in detail, as their precise determination is not required for the problems considered here; a separate analysis of these parameters based on high-frequency vibrational modes will be given elsewhere.[4] Most important for the present purpose is information on the rotational barriers that are strongly affected by the torsional and nonbonded terms in the potential function. It is just these terms that play an essential role in determining the inherent flexibility of macromolecules of biological interest.

In addition to the role of the present work in improving potential functions, it is of interest in aiding our understanding of the factors responsible for the conformational preferences and potential surfaces of the molecules considered. Although ab initio quantum mechanical calculations can be used to calculate these properties, they do not directly provide an understanding of the factors involved. This is particularly true for the higher level calculations required in many cases to obtain accurate results. Interpreting these in terms of empirical force fields can be an aid in understanding the important contributing effects. In this paper, we aim both to determine parameters for an improved force field and to interpret the influences of the different terms on the conformational properties. The methodology involves parameterizing the force field with respect to properties of the simplest members of a given series and then testing the transferability of the force field by applying it to calculate other properties of the molecules or of molecules not used in the parameterization. In some cases, predictions are made, such as transition-state geometries, and the physical origins of the energy differences are investigated.

A number of molecular mechanics force fields have been devised.[1,5–14] They are similar in character but they do contain some different energy terms that complicate comparisons. The diversity of these force fields is due in part to their being devised for different purposes, e.g., to calculate vibrational spectra, and/or structures, and/or heats of formation or vaporization. The form of the potential function used here is notable for its simplicity. This is justified by the primary field of application, which is to large molecules of biological interest. The simplicity of the force field is manifested by the absence of anharmonic coupling and the inclusion of only lowest order torsional terms for the bonding interactions. Anharmonic effects, if reproduced by the energy function, are due to intramolecular nonbonded (van der Waals and electrostatic) interactions. This paper is concerned in part with determining to what level of detail the CHARMM force field[4,11] (nonbonded interactions, together with a simple, harmonic representation of bond length and angle deformations and a symmetric torsional term) can reproduce series effects in the geometries and conformational transitions of the selected molecules. In contrast to some force fields for macromolecules,[10,11] all atoms including nonpolar hydrogens are treated explicitly.

The effect of intramolecular nonbonded interactions on rotational barriers is a recurrent theme in this paper. This can be approached via bulky group substitutions in a series for which the torsional potential of the simplest molecule has been parameterized. A well-characterized series of this type consists of the alkanes ethane, propane, and butane. Parameters obtained from ethane, propane, and butane are transferred to the calculation of the energetics of the cyclohexane ring inversion cycle and the energy minimum geometry of the overcrowded branched alkane tri-*tert*-butylmethane. In both cases, good agreement with experiment is obtained.

The study of asymmetric rotations, in which the potential energy minima are at different energies, is of particular interest. To reproduce these energy differences, some force fields include additional low-order torsional terms (e.g., 1-fold and 2-fold terms in an sp^3–sp^3 C–C torsion),[1,14] but this has not been found necessary in the calculations presented here, in which the asymmetry of the torsional potentials has been obtained from nonbonded interactions. The form of the potential function thus allows a separation of nonbonded and intrinsic torsional contributions in the case of such asymmetric rotational barriers. An accurate reproduction of the energy as a function of the central C–C bond rotation in *n*-butane is a sensitive test of the hydrocarbon part of the potential. The trans–gauche energy difference, which is almost entirely due to nonbonded interactions, is studied in detail. We find a strong electrostatic contribution to the trans–gauche energy difference that is very sensitive to the value of the atomic partial charges and the method of representation of short-range electrostatic interactions.

A series of molecules that contain sp^2 carbons attached to methyl groups are investigated. These molecules exhibit very different methyl rotational barriers. This allows us to investigate whether the potential function is sufficiently flexible to be able to be parameterized to reproduce widely varying properties within a class.

In section 2, the methodology is described. In section 3.i., the selected alkanes are investigated. The energy function is parameterized with respect to the geometries and methyl torsional energies of ethane and propane and is used to calculate the C–C rotational potential in *n*-butane, the ring inversion energetics of cyclohexane, and the energy minimum geometry of the crowded alkane tri-*tert*-butylmethane. In section 3.ii., energy minimum geometries and methyl rotational barriers are calculated for the molecules containing methyl groups attached to double bonds—acetaldehyde, propene, acetone, 2-methylpropene, and *cis*-butene. The conclusions are stated in section 4. The results of general interest described here are being used also in the determination of an accurate all-atom force field for molecules of biological interest.[4]

2. Methods

Form of Potential Energy Function. The molecular mechanics program used here (CHARMM) and an early version of the potential energy function have been described previously.[11] Compared to most small molecule force fields, the potential function in eq 1 is notable for its simplicity. The form of the potential energy function is

$$V = \sum_{\text{bonds}} k_b(b - b_0)^2 + \sum_{\text{angles}} k_\theta(\theta - \theta_0)^2 + \sum_{\text{dihedrals}} k_\phi[1 + \cos(n\phi - \delta)] + \sum_{\text{impropers}} k_\omega(\omega - \omega_0)^2 + \sum_{i,j}[4\epsilon_{ij}(\sigma_{ij}/r_{ij})^{12} - (\sigma_{ij}/r_{ij})^6] + \sum_{i,j}\frac{332q_iq_j}{r_{ij}} sh(r_{ij}^2, r_{\text{off}}^2)e14(i,j) \quad (1)$$

where

$$sh(r_{ij}^2, r_{\text{off}}^2) = \begin{cases} 0, & r_{ij}^2 > r_{\text{off}}^2 \\ 1 - \dfrac{r_{ij}^2}{r_{\text{off}}^2} & r_{ij}^2 < r_{\text{off}}^2 \end{cases} \quad (2)$$

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In eq 1, b, θ, ϕ, and ω are the bond lengths, angles, dihedrals, and improper torsions and b_0, θ_0, and ω_0 are the reference values for these properties. The force constants associated with these terms are k_b, k_θ, k_ϕ, and k_ω. For the intrinsic torsions, n is the symmetry number of the rotor (e.g., 3 for a methyl group) and δ is the phase angle. Bond length and angle deviations are represented by harmonic restoring forces with neither anharmonic terms, such as Morse functions,[1,17] nor 1,3 or 1,4 coupling, such as Urey–Bradley terms.[18,19]

In spectroscopic analyses, the effective Hamiltonian for torsional motion is conventionally expressed as a Fourier expansion:

$$V(\phi) = \sum_k V_{kn}[1 - \cos(kn\phi)] \qquad (3)$$

where n is the symmetry number of rotor and $k = 1, 2, 3, ...$ For a perfectly symmetrical 3-fold barrier, such as ethane, $V(\phi)$ is completely described by an expansion with V_3, V_6, etc. The addition of a V_6 term does not change the height of a 3-fold barrier, as V_6 is zero at the maxima and minima, but it does change the shape of the potential well,[20] and thus the librational torsional frequency. A positive V_6 narrows the well and broadens the maximum. If the rotor is a methyl group, V_6 is very much less than V_3, with V_6/V_3 typically less than 0.01.[21,22] The intrinsic torsional potential adopted in CHARMM is a simple 3-fold or 2-fold sinusoid depending on the symmetry of the torsion considered; i.e., V_6 terms are not explicitly included. Some molecular mechanics force fields include terms of lower order than the rotor symmetry. In certain cases, this allows a correct representation of asymmetric rotational potentials.[1,59,60] In the current work, we find that such asymmetry follows naturally from the explicit inclusion of nonbonded interactions, and such low-order terms are not included.

The 1,4 dependence of the torsional force constants is included for the unsaturated molecules. This means that, in contrast to the previous version of the force field[11] where for atoms A–X–Y–B the torsional term is independent of the nature of atoms A and B, dependence on A and B is included. All possible sets of bonded atoms are included in the dihedral energy computation so that, e.g., for an sp^3 rotation there are nine contributing dihedral terms in the energy function. This symmetrizes the torsional part of the energy calculation and allows for 1,4 dependence to be included. Improper torsional terms are employed as defined in ref 11 to maintain planarity of the sp^2 carbon groups.

The nonbonded terms in eq 1 are pairwise additive and consist of a 12–6 Lennard-Jones van der Waals term and a Coulombic term representing electrostatic interactions between atomic partial point charges. These nonbonded interactions are included for 1,4 (vicinal) or higher order atom pairs. The quantities r_{ij}, ϵ_{ij}, σ_{ij}, q_i, and q_j are the nonbonded distance, the Lennard–Jones well depth, the Lennard–Jones diameter, and the charges for atom pairs i and j. The reduction factor $e14(i,j)$ in eq 1 is 1 for all 1,4 atom pairs (pairs separated by a dihedral angle). The effect of reducing the 1,4 electrostatic interactions is discussed in the Results. A distance-independent dielectric constant of 1 is assumed. The electrostatic interactions are truncated at a distance ($r_{\rm off}$) of 7.5 Å, by "shifting" the potential, as described by eq 2, in such a way that the first derivative is also equal to zero at this distance.[11] Although for small molecules it is computationally inexpensive to perform the calculations without electrostatic truncation, this becomes necessary in protein simulations. For the problems reported here, the effect of truncating the electrostatic interactions on the results obtained is small. Cases where a noticeable effect is seen are discussed in the text.

Unlike the published version of the CHARMM potential function,[11] there is no explicit hydrogen-bonding term in the potential function. As described previously,[23] this interaction can be represented by a combination of electrostatic and van der Waals interactions. A further improvement is the explicit inclusion of all the atoms. In a previous published version,[11] nonpolar hydrogens were incorporated with the heavy atom to which they are attached in an "extended atom" representation, although an all-atom force field has been available.

Calculational Procedure. The energy function was employed to calculate minimum energy geometries and conformational transitions for the molecules considered. Gas-phase experimental values for bond lengths and angles of simple organic molecules are usually obtained by using electron diffraction or microwave spectroscopy. When considering bond length variations of the order of 0.01 Å, the method of measurement becomes significant.[24] The equilibrium structure, r_e, corresponds to the hypothetical 0 K geometry neglecting zero-point energy.[25] This is the quantity calculated by ab initio quantum mechanics, and is accessible using molecular mechanics by energy minimization. Unfortunately, r_e has been extracted experimentally for only a few small molecules.[24]

The quantity r_g is the average value of an instantaneous internuclear distance. It is normally derivable from electron diffraction, and is usually considered to be the best quantity for comparison with molecular mechanics bond lengths. Bond anharmonicity changes mean nuclear positions from their minimum energy positions, so r_g is not exactly the same as r_e. The difference between r_g and r_e can be considerable, especially for CH bonds. For example, in methane, for which calculations of the r_e structure have been made, the r_e structure gives the CH bond lengths as 1.084 Å whereas the r_g lengths are 1.106 Å[26]). In the absence of r_e structures for the molecules of interest, we parameterize our force field to provide r_g minimum energy bond lengths; in most cases, the difference is within the uncertainty of the force field.

The r_g geometry is inconvenient for a description of bond angles, as geometrical inconsistencies are introduced. Take, for example, an angle that is linear in the equilibrium structure. Displacements from the energy minimum always reduce the 1,3 distance. In this case, the mean internuclear distance will correspond to a bent angle. The spectroscopically derived r_z coordinates give the distance between mean positions of atoms in the ground vibrational state.[24] As far as possible, we compare our calculated angles with r_z experimental results.

Initial parameters for the energy function were taken from a previous version of the all-atom potential.[11,27] Except where specified elsewhere

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in the text, these parameters were unchanged in the calculations; all of the final values, whether unchanged or not, are given in Tables XIX–XXIV. For a given series, the bond length and angle equilibrium values were manually adjusted where necessary to reproduce experimental geometries of the simpler molecules on energy minimization. The intrinsic torsional term was adjusted such that, together with the relevant nonbonded contribution, the experimental methyl rotational barrier of the simplest molecule was accurately reproduced. For the alkane series, the resulting parameters were transferred where possible to more complicated members of the series (e.g., propane, butane). Some new parameter adjustments were necessary for these molecules, such as the CCC angle in propane. In certain cases, the whole energy function can be transferred without modification to more complicated molecules in the series. Examples of this are the applications to the ring inversion energetics of cyclohexane and the tri-*tert*-butylmethane energy minimum geometry. For the calculations on the molecules with methyl groups bonded to sp^3 carbons, the aim was to see if the potential function is sufficiently versatile to reproduce widely varying methyl rotational barriers within the class of molecules. Nonbonded parameters for the main part were transferred from the previous potential[11,27] and were not optimized. Exceptions are detailed in the text. For example, it is found that there is a strong dependence on electrostatics for the difference in potential energy between the gauche and trans conformers of *n*-butane. For this case, an improved representation of the electrostatic potential energy was found.

Potential energy differences for conformational transitions were calculated by using two different methods. The simplest method of calculation for such barriers is rigid rotation of the appropriate torsional angles starting from the minimum energy structure. The transitions are also calculated adiabatically, with the energy at the top of the barrier calculated by constraining the appropriate torsions to maintain the molecule in the transition state, while minimizing the energy with respect to the other degrees of freedom. These two methods represent time scale extrema. A rigid rotation corresponds to the dynamical approximation that the transition is very fast compared to the relaxation of the other degrees of freedom, whereas it is assumed to be very slow in the adiabatic approximation. For most studies, the latter approximation is better.

3. Results

3.i. Alkanes. The alkanes represent an important set of compounds for study in establishing a molecular mechanics force field for proteins. Aliphatic groups are present in most amino acid side chains. Moreover, accurate theoretical and experimental data are available for a range of conformational properties that provide a good basis for determining and testing the form and parameters of a potential energy function. We first study energy-minimized geometries as a function of chain length for the alkanes methane, ethane, propane, and *n*-butane. Methyl rotational barriers are parameterized for ethane and propane, and the relationship between nonbonded and intrinsic contributions to the adiabatic and rigid rotational barriers are examined. The asymmetric central C–C butane rotational potential is calculated and compared with experimental, molecular mechanical, and quantum mechanical results. The energy minimum cyclohexane geometry and its chair–transition state–twist boat ring inversion energetics are examined. Finally, the equilibrium geometry of tri-*tert*-butylmethane is determined as a test of the ability of the force field to represent the geometry of an overcrowded hydrocarbon.

For the alkane calculations only a small number of parameters are used. These consist of the reference values and force constants for CH and CC bonds, HCH, HCC, and CCC angles, and the 3-fold C–C intrinsic torsional barrier, Lennard-Jones parameters for the carbon and hydrogen atoms, and a simple representation of the partial charges in which all hydrogen atoms have the same value (0.09 electrons) and the carbon charges are correspondingly negative so as to maintain neutrality of the CH, CH$_2$, and CH$_3$ groups. For the most part, the parameters were derived from calculations on ethane and propane, the exception being the partial charges, to which the butane gauche–trans energy difference was found to be very sensitive; its value was used in the refinement.

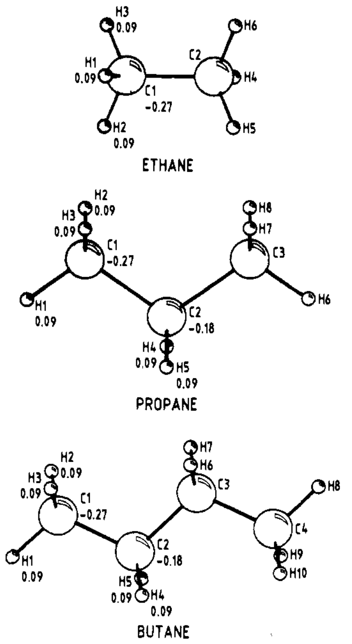

Figure 1. Energy minimum geometries, partial charges, and atom names of ethane, propane, and butane.

Table I. Energy-Minimized and Experimental Geometries for Ethane

	calcd	exptl[69]
C1–H1	1.101	1.112 (0.001)
C1–C2	1.538	1.534 (0.001)
H1–C1–H1	108.6	107.5 (1.0)
H1–C1–C2	110.3	111.2 (0.3)

Table II. Energy-Minimized and Experimental Geometries for Propane

	calcd	exptl[70]
C1–H1	1.101	1.107 (0.005)
C2–H4	1.103	
C1–C2	1.532	1.533 (0.003)
H1–C1–H2	108.72	107.9 (0.2)
H1–C1–H3	108.72	
H2–C1–H3	108.67	
C1–C2–C3	111.5	112.0 (0.2)
H4–C2–H5	107.6	107.8 (0.2)
C1–C2–H4	109.4	
C1–C2–H4	109.4	
H1–C1–C2	110.26	
H2–C1–C2	110.21	
H3–C1–C2	110.21	

Methane, Ethane, Propane, and *n*-Butane. Energy-Minimized Geometries. Calculation of the methane structure is simple because of the exclusion of 1,3 nonbonded interactions in the potential function. Thus, the only terms contributing to the energy are those of the HCH angles and CH bonds. These two terms are independent of each other, and so the methane minimizes to tetrahedrality and the CH reference bond lengths, 1.100 Å, in comparison to the experimental methane r_g CH lengths of 1.106 Å.[26] The energy minimum geometries, nomenclature, and partial charges of ethane, propane, and butane are shown in Figure 1. The values for the minimum energy geometries of these molecules are given in Table I–III.[117] The calculated geometries reproduce all bond lengths and angles in ethane, propane, and butane to within 0.01 Å and 1° of the experimental values, respectively. Characteristic bond angle trends in going from CH$_4$ to CH$_3$ to CH$_2$ are well reproduced, despite the absence of extra, anharmonic and coupling terms employed in other force fields.[28,1] The HCH and HCC angles narrow by ~1° going from CH$_3$ to CH$_2$ in agreement with experiment and previous calculations.[28,29] CH bond length trends are qualitatively correct but quantitatively too small, lengthening by 0.001 Å from CH$_4$ to CH$_3$ and 0.002 Å from CH$_3$ to CH$_2$, compared with experimental values of ~0.005 Å for each transition.[28] Also reproduced is the CCC angle widening effect going from propane (111.5°) to butane (112.1°) although there is some evidence that the butane CCC angle might be slightly larger than calculated here; high-level quantum mechanical

Table III. Energy-Minimized and Experimental Geometries for Butane (Trans Conformer)

	calcd	exptl[137]
C1-H1	1.101	
C2-H4	1.102	
⟨C-H⟩		1.117 (0.005)
C1-C2, C3-C4	1.534	
C2-C3	1.530	
⟨C-C⟩	1.531	
H1-C1-H2	108.7	
H1-C1-C2	110.2	
H4-C2-C3	109.2	
H4-C2-C1	109.4	
H4-C2-H5	107.6	
C1-C2-C3	112.1	113.8 (0.4)

calculations estimate the value as 112.9–113.1.[57b,c]

Aliphatic Alkanes. Methyl Torsional Barriers. The intrinsic torsional term for C–C rotation was parameterized to produce agreement with the ethane barriers, and then transferred to all other studied alkanes. In the calculations, it was not necessary to introduce dependence of the torsional term on the specific 1,4 atoms (C or H). The fitted adiabatic ethane rotational barrier is 2.95 kcal/mol; this agrees to within experimental uncertainty with the measured value of 2.93 ± 0.03 kcal/mol.[33] The calculated barrier is dominated by the intrinsic torsional term, which is 2.826 kcal/mol. The nonbonded contribution is only about 0.1 kcal/mol, most of which is due to van der Waals H···H repulsions. As a result, the rigid rotational barrier is only 0.0015 kcal/mol higher than the adiabatic barrier. In the adiabatic torsion, small geometry changes were noticed in the eclipsed conformer, the CC bond lengthening by 0.002 Å to 1.540 Å, the HCC angles increasing by 0.1° to 110.4°, and the HCH angles decreasing by 0.1° to 108.5°. These small geometric changes can be compared with the results of two recent quantum mechanical calculations, which have estimated the eclipsed C–C bond lengthening to be 0.010 Å[34] and 0.15 Å[35] and the HCC angle widening to be 0.4°.[34,35] Both of these calculations predict effects in the same direction but larger than those obtained from the empirical potential.

As propane has two close methyl groups, one can investigate the coupling between their rotational barriers. The lowest energy conformer of propane has both methyls staggered. The adiabatic energy difference between this and the conformer with one methyl staggered and one eclipsed (the V_1 barrier) is calculated to be 3.09 kcal/mol. The difference between the conformer with both methyls eclipsed (the high-energy state) and that with one eclipsed and one staggered, the V_2 barrier, is calculated to be 3.33 kcal/mol adiabatically, whereas the rigid barrier is 3.52 kcal/mol. The microwave data of Hirota et al.[35] was analyzed by Hoyland[36] assuming rigid rotation, with resulting values for V_1 and V_2 of 3.12 and 3.84 kcal/mol, respectively. The V_1 barrier is in good agreement with the present value, but the V_2 barrier is about 0.3 kcal/mol higher than the corresponding (rigid) value calculated here.

In the unrelaxed high-energy V_2 transition state, two H atoms, one on each methyl group, are the source of strong van der Waals repulsion. In the relaxed V_2 transition state, three angles absorb most of the angle strain needed to reduce this repulsion; the C–C–C angle opens by 1.8° to 113.24°, and the two H–C–C angles to which the two interacting hydrogens belong aid their separation by opening by 0.9° to 111.2°. The two methyl hydrogens are separated by 2.10 Å in the relaxed structure, relative to 2.00 Å in the rigid rotation structure. The van der Waals energy is thus reduced by 0.38 kcal/mol. This reduction is accompanied by an increase of 0.10 kcal/mol in the electrostatic energy.

Quantum mechanical calculations indicate that the principal interaction giving rise to the internal rotation barrier in ethane is CH bond overlap (exchange) repulsion.[38,39] In the empirical potential, this effect is represented by the intrinsic torsional term. The predominance of this term is consistent with the idea that 1,4 Coulombic interactions do not play a major role in the ethane barrier.[38–40] Electrostatics does not play a major role in the propane V_1 torsion but does have a significant effect on the propane V_2 and butane gauche–trans (see next section) energy differences. In the propane V_2, the electrostatic contribution to the adiabatic barrier is 0.145 kcal/mol, i.e., 33% of the residual nonbonded contribution after energy minimization. Due to its shallow distance dependence, the electrostatic contribution cannot be easily reduced by energy minimization and as such is relatively independent of the method used to calculate the barrier, adiabatic or rigid.

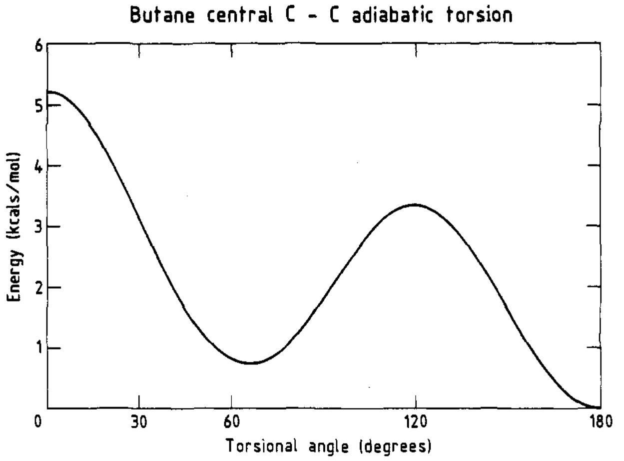

Figure 2. Potential energy as a function of the adiabatic central C_2–C_3 rotation in *n*-butane.

***n*-Butane Torsions.** The central C–C torsion in *n*-butane is fundamental to our understanding of the interplay of short-range nonbonded and intrinsic torsional forces in the empirical potential. The calculated potential energy as a function of C–C torsion is plotted in Figure 2, in which the highest energy (cis or syn) conformation is at 0° and the lowest (trans or anti) at 180°. The other energy minimum is the gauche conformation, near 60°.

The energy differences between the various extrema in Figure 2 have been a subject of discussion over the years. In particular, the origin and phase dependence of the gauche–trans (sometimes called gauche–syn) energy difference have been in dispute.[30,41–61] In the present formulation, this energy difference is determined almost completely by nonbonded interactions, as the intrinsic torsional energy is zero in the trans conformer and very small in the gauche conformer. Gas-phase measurements have given values around 0.7–1.0 kcal/mol for the gauche–trans energy difference[30,41–45] whereas liquid data suggests 0.5–0.6 kcal/mol.[46,47] The existence and possible cause of liquid-phase barrier lowering has been debated.[48–54] More recently several high-level quantum mechanical calculations have been performed. These place the gauche–trans barrier before correction for zero-point energy differences at 0.5–0.6 kcal/mol[55] and 0.75 kcal/mol.[56] The adiabatic value obtained here is 0.70 kcal/mol.

An approach to model the gauche–trans conformational change involves incorporating low-order terms into the torsional potential.[59,60] Alternatively, for force fields such as the present one, the inclusion of short-range electrostatic interactions suffices to explain the energy difference.[61,9] We find that the value obtained for the trans–gauche energy difference is very sensitive to the electrostatic model used, in particular, the values of the partial charges and whether the 1,4 electrostatic interactions are reduced. The sensitivity to partial changes was explored by the following approach. With the simplifying assumption of electrical neutrality of the methyl and methylene groups, the hydrogen partial charges were changed by 0.01 electrons, with a corresponding opposite change of 0.02 electrons in the CH_2 carbons and 0.03 electrons in the CH_3 carbons. Such small changes produced a gauche–trans energy change of ~0.1 kcal/mol. The final hydrogen partial charges of 0.09 lead to a 70% electrostatic contribution (0.52 kcal/mol) to the gauche–trans difference. This compares with

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Table IV. Major Gauche Minus Trans Electrostatic Energy Differences for *n*-Butane

	adiabatic	rigid
1,5 methyl H···central H	−1.383	−1.496
1,5 methyl H···methyl C	−4.059	−4.327
1,6 methyl H···methyl H	2.217	2.372
1,4 methyl C···methyl C	1.961	2.091
1,4 methyl C···central H	1.529	1.409
1,4 central H···central H	0.270	0.253

the small van der Waals contribution of 0.09 kcal/mol. A similar, relatively large electrostatic contribution (0.39 kcal/mol) has been obtained in a calculation using the potential of Lifson and Warshel.[59] A small effect on the calculated energies is seen if the method of truncation of the electrostatic interactions is varied. A calculation of the adiabatic gauche–trans energy difference without truncation of the electrostatic interactions results in a value of 0.64 kcal, compared with 0.70 kcal/mol from the "shift" method. The electrostatic contribution to this is 0.46 kcal/mol compared with 0.52 kcal/mol from the shift method. The major electrostatic contributions to the 0.70 kcal/mol energy difference are listed in Table IV. This table shows that the net electrostatic energy difference is far less than most of the individual contributing interactions. Methyl–methyl hydrogen atom repulsions are the single biggest contributor to the calculated energy difference. As in the propane calculation, minimization in the gauche conformer does not significantly alter the electrostatic energies. Table IV suggests that there are many different interactions responsible for the gauche–trans energy difference.

It is of interest to consider the 1,4 electrostatic interactions separately, with a view to gaining insight concerning the effects of their scaling. We find that the effect of 1,4 scaling is to strongly affect the electrostatic balance in the molecule. When the 1,4 electrostatic interactions are multiplied by 0.5, the energy-minimized gauche conformer becomes 1.20 kcal/mol *lower* in energy than the trans conformer, a result in qualitative disagreement with experiment. The reasons for this discrepancy become apparent when the contribution of the electrostatic terms themselves to this energy difference is examined. When not scaled, the 1,4 electrostatic interactions stabilize the trans conformation by 3.7 kcal/mol over the gauche conformation. This stabilization is reduced to 1.85 kcal/mol when the 1,4 electrostatic interactions are scaled by 0.5.

The gauche energy minimum is thought to be near but not exactly equal to 60°. Electron diffraction values of 67.5° ± 1.1°[63] and 72.4° ± 5°[44] and a Raman value of 62° ± 1°[43] have been reported. Quantum mechanical estimates for the angle are 65–66°.[55,56] The calculated value for this is 66.0° ± 0.1°, in good agreement with the previous estimates. The calculated potential energy curve has a very small gradient around the minimum, a 1° change in the torsional angle producing only a 0.003 kcal/mol energy difference after minimization. An accurate estimation of such small energy differences is difficult, and so there is some uncertainty in the 66° result. Correspondingly, the shallowness of the potential energy curve suggests that the distribution of the gas-phase gauche configurations around the gauche minimum should be rather broad.

A twist of the terminal methyls away from the standard eclipsed conformation in the gauche conformer has been suggested. Quantum mechanical calculations have estimated this twist to be 3–4°[55] and 5°.[64] Our results give a value of 2.2°.

There has been some recent discussion concerning the value of the cis–trans energy difference (sometimes called syn–anti).[56,57] Two recent high-level quantum mechanical calculations give values of 4.89 kcal/mol[57] and 6.34 kcal/mol.[56] These calculations included large basis sets, geometry optimization, and electron correlation corrections, and yet, as evidenced by the difference between the above results, the values still have not converged. With use of our force field, the adiabatic cis–trans energy difference is 5.1 kcal/mol. The cis conformer is under considerable nonbonded strain due to the close approach of the two methyl groups. The rigid barrier is calculated to be 7.0 kcal/mol, 3.3 kcal/mol of which is van der Waals energy. Energy minimization resulted in a decrease of the van der Waals energy by 2.6 kcal/mol and an increase of the electrostatic energy by 0.3 kcal/mol. The nonbonded contribution to the adiabatic cis–trans energy difference is composed of 1.1 kcal/mol electrostatic and 0.8 kcal/mol van der Waals energies. The main geometric change in the cis conformer is a widening of the CCC angle. The calculated result is 3.5°, in agreement with quantum mechanical estimates.[55-57]

Table V. Energy-Minimized and Experimental Geometries of Cyclohexane in the Chair Conformation

	calcd	exptl[67]
C1–H1	1.101	1.121 (0.004)
C1–C2	1.536	1.536 (0.002)
C1–C2–C3	111.4	111.4 (0.2)
H1–C1–C2 (equatorial H)	109.8	
H2–C1–C2 (axial H)	108.9	
H1–C1–H2	107.9	
C1–C2–C3–C4	55.0	54.9
H1–C1–C2–C3	176.6	
H2–C1–C2–C3	−65.2	

Table VI. Minimized Energy Geometry of Cyclohexane in the Twist Boat Conformation

C1–C2, C4–C5	1.534	C1–C2–C3–C4	29.56
C2–C3, C3–C4, C5–C6, C6–C1	1.542	C2–C3–C4–C5	29.56
C1–H1	1.101	C3–C4–C5–C6	−61.15
C1–C2–C3, C6–C1–C2	111.8	C4–C5–C6–C1	29.56
C3–C4–C5, C4–C5–C6	111.8	C5–C6–C1–C2	29.56
C2–C3–C4, C5–C6–C1	113.1	C6–C1–C2–C3	−61.15

Table VII. Minimized Energy Geometry of Cyclohexane in the Transition State

C1–C2	1.551	C4–C5–C6	109.81
C2–C3	1.545	C5–C6–C1	114.85
C3–C4	1.528	C6–C1–C2	118.22
C4–C5	1.523	C1–C2–C3–C4	−7.26
C5–C6	1.528	C2–C3–C4–C5	47.67
C6–C1	1.545	C3–C4–C5–C6	−68.67
C1–C2–C3	118.20	C4–C5–C6–C1	47.34
C2–C3–C4	114.81	C5–C6–C1–C2	−6.93
C3–C4–C5	109.77	C6–C1–C2–C3	−13.53

Table VIII. Energy Contributions to Cyclohexane Ring Inversion Energy Differences

	twist boat–chair	transition state–chair
total	6.84	11.50
bonds	0.10	0.17
angles	0.02	1.74
dihedrals	5.22	8.22
van der Waals	1.06	0.28
electrostatic	0.44	1.08

Finally, the adiabatic trans–gauche (120°) barrier is calculated to be 3.32 kcal/mol, in good agreement with the quantum mechanical estimates of 3.1–3.3 kcal/mol[55] and 3.36 kcal/mol.[57] Our calculation of the rigid barrier gave a value of 3.45 kcal/mol.

Cyclohexane. The parameters derived from ethane, propane, and butane were applied without modification to cyclohexane. The chair conformation of cyclohexane, which is the energy minimum for this molecule, is an example where nonbonded repulsions produce a slight strain on dihedrals, angles, and bonds. We found that our alkane force field accurately reproduces these effects. In addition, we also calculated the conformational pathway energetics and geometry changes in going from the chair to the twist boat.

In the experimentally derived cyclohexane chair geometry, the CCCC torsional angles are 54.9° and the CCC bond angles are

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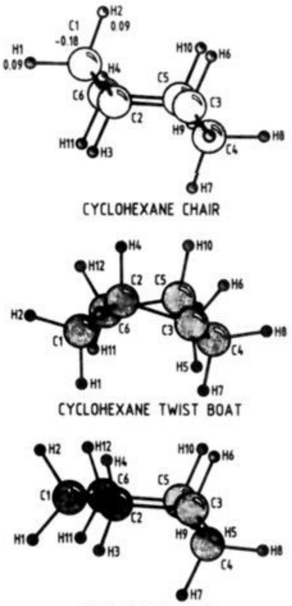

Figure 3. Chair, transition-state, and twist boat minimum energy geometries of cyclohexane.

111.4° ± 0.2°.[67] The r_g length for the CC bond is 1.536 Å, slightly longer than in ethane[68,69] and propane.[70] The calculated geometry, by using the parameters derived above, is given in Table V. The energy minimum chair structure is in excellent agreement with the experimental quantities. The calculated geometries of the chair, twist boat, and sofa conformations are shown in Figure 3.

In Tables VI and VII are listed the calculated geometries and energies associated with other points on the ring inversion pathway. The calculated twist boat conformation exhibits some CCC angle strain (a widening of two CCC angles to 113.1°), and four CC bonds lengthen to 1.542 Å while two shorten slightly to 1.534 Å. The twist boat–chair conformational energy difference is calculated to be 6.8 kcal/mol, the majority of which arises from intrinsic torsional (5.2 kcal/mol) and van der Waals (1.1 kcal/mol) contributions. This is somewhat higher than experimental values of 4.8–5.9 kcal/mol[71-74] and theoretical results of 5.6–6.05 kcal/mol.[75-77] The energy barrier associated with the twist boat–chair conversion is calculated to be 11.5 kcal/mol, in comparison with previous estimates of ~10–11 kcal/mol[76-79] (see Table X). The calculated minimum energy transition-state bond angles are unequivalent with two CCC angles widened by 5° from their reference value; the transition state possesses considerable bond angle strain (1.74 kcal/mol).

Tri-*tert*-butylmethane (TTBM) Geometry. TTBM is of particular interest in the study of the influence of intramolecular forces on molecular geometry, as it is an example of a highly crowded molecule. Several close H···H approaches are seen in the electron diffraction structure.[80] Structural distortions result, the most extreme example of which is the C_t–C_g (tertiary carbon–quaternary carbon) bond, which stretches to 1.611 Å compared to 1.534 Å in ethane and 1.533 Å in butane. Also, the C_q–C_t–C_q angles are opened to 116.0° (compared to 112.0° in propane) and the C_m–C_q–C_m (methyl carbon–quaternary carbon–methyl carbon) angles are closed to 105.7°. The torsional angles are also significantly displaced from the staggered value.

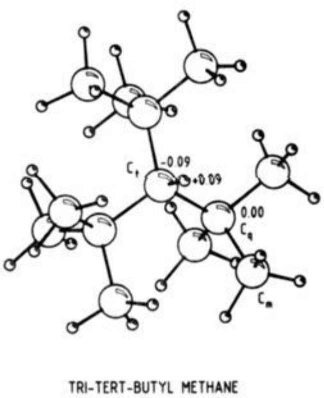

Figure 4. Energy minimum geometries, atom names, and partial charges of tri-*tert*-butylmethane.

Table IX. Energy-Minimized and Experimental Geometries for Tri-*tert*-butylmethane

	calcd	exptl[80]
$\langle C_t–C_q \rangle$	1.606	1.611 (0.005)
$C_q–C_m$	1.541, 1.533, 1.532	
$\langle C_q–C_m \rangle$	1.535	1.548 (0.002)
$C_q–C_t–C_q$	115.8	116.0 (0.4)
$C_m–C_q–C_t$	113.5, 113.9, 112.1	
$\langle C_m–C_q–C_t \rangle$	113.2	113.0 (0.2)
$C_m–C_q–C_m$	108.5, 105.9, 102.1	
$\langle C_m–C_q–C_m \rangle$	105.5	105.7 (0.2)
$C_q–C_m–H_m$	110.7, 109.9, 111.3 110.2, 110.2, 111.2 111.3, 111.2, 110.2	
$\langle C_t–C_m–H_m \rangle$	110.7	114.2 (1.0)
$H_t–C_t–C_q–C_m$	15.0, 13.7, 18.4	
$\langle H_t–C_t–C_q–C_m \rangle$	15.7	10.8 (0.5)
$C_t–C_q–C_m–H_m$	14.0, 16.6, 20.5	
$\langle C_t–C_q–C_m–H_m \rangle$	17.0	18.0 (6.0)

The energy-minimized geometry is shown in Figure 4 and listed in Table IX together with the electron diffraction results. Excellent agreement with experiment is seen for most of the geometrical parameters. The C_t–C_q bond length is 1.606 Å, compared to previous calculations of 1.578 Å without Morse functions[81] and 1.595 Å[82] and 1.601 Å[28] with Morse functions. Excellent agreement is also seen for both the stretched C_q–C_t–C_q angles and the relatively undistorted C_m–C_q–C_t angles. The agreement between experiment and calculation for $\langle C_m–C_q–C_m \rangle$ is surprisingly good in view of the large distortion from the reference value for this angle (around 7°) and the wide variations in the individual calculated angles. The torsional angle displacements from the staggered conformation are also in good agreement with experiment. Disagreements between the calculations and experiment are found for the methyl groups. The calculated value of $\langle C_q–C_m \rangle$ is about 0.01 Å less than the experimental average. Also, the $\langle C_q–C_m–H_m \rangle$ angle is far less strained in the calculated structure (110.7°) than the experimental one (114.2° ± 1.0°), the latter being derived by imposing local C_3 symmetry on the CC_3 and CH_3 segments of the *tert*-butyl groups.

It has been previously suggested that anharmonic terms in the bond length potential are necessary to reproduce the highly stretched C_q–C_t TTBM bond lengths.[28,82] The results presented

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Table X. Calculated and Experimental Conformational Energy Differences in Some Simple Alkanes[a]

	calcd	exptl
ethane methyl rotation	2.95	2.93 (0.02)
propane V_1 methyl rotation	3.09	3.12
propane V_2 methyl rotation	3.52[b]	3.84[b]
butane gauche–trans	0.70	0.5–0.9
butane cis–trans	5.1	4.5–6.0
butane 120°–trans	3.3	3.3
cyclohexane twist boat–chair	6.8	6
cyclohexane transition state–chair	11.5	10–11

[a] The references for the experimental data are given in the text and other tables. [b] Calculation and experimentally derived values assume rigid rotation.

here indicate that this is not the case, as a good representation of the TTBM structure is obtainable simply through the influence of nonbonded effects with parameters for harmonic bond length potentials determined for unstrained molecules.

To investigate the role of the various energy terms in the C–C bond lengthening effect, minimizations were performed, varying terms in the energy function. The results of these calculations indicate that the van der Waals repulsions are of primary importance. When these are removed, the C–C bond relaxes back to 1.526 Å, which is close to the reference value of 1.530 Å. In contrast, when the electrostatic interactions are removed, the C–C length increases to 1.609 Å. With 50% reduction of the 1,4 electrostatic interactions, the C–C length increases to 1.612 Å. The C–C lengthening appears to be a sensitive test of the balance between the bond stretching force constant and the van der Waals interaction term in the present force field. That the results are in good agreement with experiment in reproducing the bond length is evidence for the soundness of the potential.

Summary of Alkane Results. Table X lists the calculated and experimental conformational energy differences discussed in this section. The good agreement between the two, and between experimental and calculated geometries of simple aliphatic alkanes, the crowded aliphatic alkane TTBM, and the cyclohexane ring, demonstrates the accuracy and transferability of the CHARMM energy function when applied to such problems, with a small number of parameters and no anharmonic components to the bond stretching and angle bending terms. For the calculations on other classes of molecules presented below, the parameters for the hydrocarbon moiety were taken from the above analysis and were applied unchanged.

3.ii. Molecules with Methyl Groups Bonded to sp^2 Carbons. The energy minimum geometries and methyl rotational barriers are studied in molecules possessing methyl groups attached to C=C or C=O bonds. In contrast to the alkanes, a methyl group attached to an unsaturated double bond prefers a conformation in which one of its CH bonds eclipses the multiple bond. The molecules studied here are acetaldehyde (CH_3CHO), propene ($CH_3CH_2=CH_2$), acetone (CH_3COCH_3), 2-methylpropene ($(CH_3)_2CH=CH_2$), and *cis*-2-butene ($CH_3CH=CHCH_3$).

The simpler of the above molecules, acetaldehyde and propene, contain one methyl group, and have rotational barriers of 1.168 ± 0.030 kcal/mol[83,84] and 1.997 ± 0.002 kcal/mol,[85,86] respectively. The difference between these two barriers has been ascribed quantum mechanically to an increased electron density at the central carbon in propene, leading to an increase in the exchange (overlap) terms that cause the barrier.[35] Methyl substitution raises the barrier to 2.12 ± 0.02 kcal/mol in the case of 2-methylpropene[87] (2.30 kcal/mol according to far-infrared measurements[88]) but lowers it in the case of acetone to 0.78 kcal/mol.

Table XI. Energy-Minimized and Experimental Geometries of Acetaldehyde

	calcd	exptl[115-117]
C–O	1.211	1.208 (0.003)
C–C	1.512	1.514 (0.005)
C–H4	1.111	1.1237 (0.0012)
C–C–O	120.7	124.72 (0.17), 123.8 (0.2)
C–C–H4	117.1	113.93 (0.22)
O–C–H4	122.2	
H3–CM–C–O	119.5	120.88 (0.05)

Table XII. Energy-Minimized and Experimental Geometries of Acetone

	calcd	exptl[117,118]
CM—C	1.503	1.517 (0.003), 1.516 (0.004)
C=O	1.207	1.210 (0.004), 1.211 (0.004)
CM—C—CM	116.3	116.0 (0.2)
CM—C=O	121.8	122.0 (0.2)

Table XIII. Energy-Minimized and Experimental Geometries of Propene

	calcd	exptl[119,120]
CM–C1	1.528	1.506 (0.003)
C1–H4	1.105	1.104 (0.010)
C1–C2	1.335	1.342 (0.002)
C2–H5 (H5 eclipses Me H)	1.1010	
C2–H6 (H6 eclipses CH H)	1.1008	
CM–C1–C2	124.61	124.3 (0.3), 124.3 (0.4)
CM–C1–H4	114.60	116.7 (0.3)
H4–C1–C2	120.78	119.0 (0.3), 121.3 (1.4)
H5–C2–C1	120.86	120.5 (0.3)
H6–C2–C1	121.16	121.5 (0.3)
H5–C2–H6	117.98	118.0 (0.3)

Table XIV. Energy-Minimized and Experimental Geometries of 2-Methylpropene

	calcd	exptl[121]	exptl[122]
CM–C1	1.516	1.507 (0.003)	1.508 (0.002)
C1–C2	1.333	1.330 (0.004)	1.342 (0.003)
C2–H4	1.099	1.088 (0.002)	1.095 (0.020)
C2–H5	1.099	1.088 (0.002)	1.095 (0.020)
CM1–C1–C2	123.63		122.2 (0.2)
CM2–C1–C2	123.63		
CM1–C1–CM2	112.74	115.3 (0.1)	
C1–C2–H4	120.89		121.3 (1.5)
C1–C2–H5	120.89		121.3 (1.5)
H4–C2–H5	118.21	118.5	

Table XV. Energy-Minimized and Experimental Geometries of *cis*-2-Butene

	calcd	exptl[91]
CM–C	1.5313	1.497
C–HA	1.102	
C–C	1.337	
CM–C–C	127.4	126.7
H–C–C	119.4	
H–C–CM	113.2	
close methyl H···methyl H distance	2.04	1.93

In *cis*-2-butene, when the methyl rotors orient so as to eclipse the C=C bond, the two in-plane methyl hydrogens approach closely. Despite the resulting nonbonded repulsion, this geometry is still the minimum energy conformation.[89-91] However, the barrier is reduced to 0.747 ± 0.004 kcal/mol[90,91] compared to 1.997 kcal/mol in propene, which possesses the same 1,4 torsional atoms. This barrier reduction has been suggested to be a consequence of the in-plane methyl hydrogen nonbonded repulsions, which act out of phase with the intrinsic torsional terms[92] and

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Table XVI. Energy-Minimized Methyl Group Geometries in Unsaturated Molecules[a]

	acetaldehyde	acetone	propene	2-methylprop	*cis*-2-butene
HC in plane	1.0995	1.0987	1.1009	1.0997	1.0987
HC out of plane	1.0979	1.0974	1.1007	1.0996	1.1002
HCH involving in-plane H	109.12	109.32	108.64	108.91	108.63
HCH involving out of plane H	109.96	110.05	109.09	109.08	108.91
HCC involving in-plane H	109.00	108.89	110.21	110.21	110.87
HCC involving out of plane H	109.74	109.62	110.15	109.85	109.88
methyl tilt	0.5	0.5	−0.04	−0.3	−0.7

[a] For the methyl tilt angles, positive values indicate a tilt toward the double bond and negative values indicate a tilt away from the double bond.

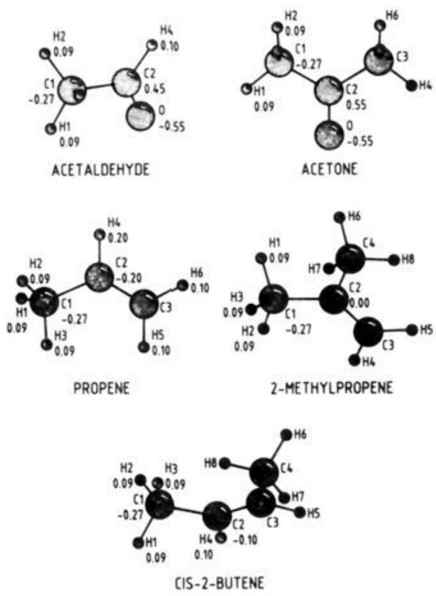

Figure 5. Energy minimum geometries, atom names, and partial charges of acetaldehyde, acetone, propene, 2-methylpropene, and *cis*-2-butene.

destabilize the minimum energy conformer.

For the calculations presented below, the initial parameters were taken from the previous force field.[27] As in the previous section, the bond length and angle reference values were in general adjusted to fit the simpler, one-rotor molecules and where possible were transferred to the two-methyl molecules. Exceptions to this are the acetaldehyde to acetone angles, discussed below, and the torsional terms. Of necessity, as explained below, the torsional parameters were fitted simultaneously to all the molecules. Indeed, it is essential to find out if the force field, through its interplay of torsional and nonbonded energy terms, can be parameterized to reproduce the disparate rotational barriers of these molecules.

Minimum Energy Geometries of Acetaldehyde, Acetone, Propene, 2-Methylpropene, and *cis*-2-Butene. The calculated energy minimum geometries of these molecules are listed in Tables XI–XV and shown, together with nomenclature and partial charges, in Figure 5. The agreement between calculated and experimental structures is generally good, the exception being the poor transferability of the aldehyde sp^2 carbon angle parameters to the acetone sp^2 carbon group. It is preferable to have a good geometry for acetone where this is important for an accurate study of methyl–methyl interactions, rather than for acetaldehyde where small geometry changes would have a negligible effect on the calculation of the relatively small 1,4 nonbonded contributions to the barrier. Thus, the angles parameters were optimized for acetone. The resulting deviation from experiment in the acetaldehyde C—C═O and C—C—H angles is about 3°.

The C—C═C alkene angle variations in these molecules provide a further test of the accuracy in modeling methyl–methyl repulsive effects on small molecule geometries. The experimental C—C═C angle in 2-methylpropene is particularly small (122.2° ± 0.2°)[93] whereas in propene it is 124.3° ± 0.4°, and in *cis*-2-butene it is increased to 126.7°. The calculated angles are 123.6°, 124.6°, and 127.4°, respectively, in good agreement with the experimental values.

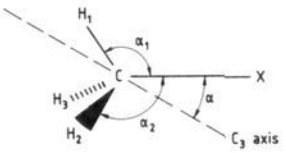

Figure 6. Definition of methyl tilt angles.

The exceptionally wide C—C═C angle in *cis*-2-butene is due to repulsion between the in-plane methyl hydrogens. It has been suggested[94] that the methyls might twist slightly, to reduce this steric repulsion. However, previous molecular mechanics minimizations[95] have resulted in the CH eclipsing the double bond at the exact minimum, despite the close H···H distance. Our calculations support this conclusion. Twisting of the methyl groups, followed by energy minimization, always recovered an exactly eclipsed energy minimum conformation. A slight twisting of the methyl groups does not significantly increase the H···H repulsion as the hydrogens move perpendicular to the line between them.[95] However, angle opening moves the hydrogen atoms away from each other along the line between them, and thus is a more effective way of separating them. Although the C—C═C angle opens to 127.4°, in good agreement with the experimental (126.7°) and quantum mechanical (127.9°,[96] 128.0°[97]) calculations, the in-plane H—C—C angle has not significantly opened, whereas in a previous molecular mechanics calculation it opened to 115.3°.[95] The close H···H distance is computed to be 2.04 Å at the energy minimum value compared to the previous molecular mechanics value of 2.16 Å and an experimental value of 1.93 Å.[91]

Methyl Group Asymmetry. The C_3 symmetry of a methyl group can be broken in a compound in which it is bonded to an asymmetric group X.[83] In particular, the methyl group can tilt, forming a nonzero angle between the methyl group symmetry axis and the C–X direction. With reference to Figure 6 the methyl tilt, α, is defined by the following equation:[99]

$$3 \cos (\alpha_1 + 2\alpha) = 4 \cos \alpha_2 - \cos \alpha_1 \qquad (4)$$

where $\alpha_1 = \angle H_1CX$ and $\alpha_2 = \angle H_2CX$.

When X possesses a lone pair of electrons, the tilt tends to be directed toward it and falls in the range 2–4°.[98,99] Another, related small effect is that the CH bond lengths in the methyl group can be different in an asymmetric environment.

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Table XVII. Methyl Rotational Barriers and Energy Components for Unsaturated Molecules[a]

	acd	ace		pro	m-prop		*cis*-2-but	
		V_1	V_2		V_1	V_2	V_1	V_2
exptl	1.16	0.78		1.99	2.2		0.74	
total	1.171	0.774	0.935	1.931	2.161	2.466	1.482	1.872
bond	0.006	−0.008	−0.024	−0.001	−0.005	−0.010	−0.014	−0.003
angle	0.038	0.040	0.096	0.014	−0.001	0.067	−0.185	−0.017
dihedral	1.205	0.702	0.702	1.998	2.118	2.118	1.998	1.998
vdW	−0.089	0.030	0.089	−0.052	0.073	0.147	−0.205	−0.117
elec	0.022	0.010	0.073	−0.029	−0.026	0.064	−0.111	0.011

[a] Key: acd = acetaldehyde, ace = acetone, pro = propene, m-prop = 2-methylpropene, *cis*-2-but = *cis*-2-butene.

As a consequence of their asymmetric environment, the methyl groups in molecules in which the methyl group is attached to an unsaturated carbon can be tilted. However, methyl tilting in these molecules is much less marked than in molecules in which the methyl group is attached to an atom possessing a lone pair of electrons (e.g., alcohols, amines).[35,105-107] Methyl tilting and methyl CH bond length asymmetry in these molecules are difficult to determine with electron diffraction or microwave data.[101,76] The direction of the methyl tilts in these molecules is unknown, although the consensus is that they are less than 1°. Infrared measurements based on the fundamentals of the CD_2H isotopomers have suggested that the out-of-plane bonds in acetaldehyde and acetone are 0.0055 and 0.0060 Å longer than the in-plane bonds.[102,103] In addition, quantum mechanical calculations[101,104] also suggest that the out-of-plane CH bonds should be about 0.005 Å longer than those in-plane.

The methyl group asymmetry in the empirical force field calculations presented here results from 1,4 nonbonded effects. The calculated asymmetries are detailed in Table XVI. The calculated methyl tilt angles and CH bond length differences are of similar magnitudes to the experimental/quantum mechanical results (methyl tilting of 0–1° and bond length differences of ~0.005 Å).[35,105-107] However, the CH bond length asymmetry is such that the in-plane bonds are longer than the out-of-plane bonds, in qualitative disagreement with the infrared and quantum mechanical results quoted above.

In *cis*-2-butene, where steric effects might be expected to tilt the methyl groups somewhat, the calculated tilt is 0.7° outward, i.e., in the direction expected from methyl–methyl repulsion. This compares with measured values of 5° outward,[108] 1° inward,[91] and the previous molecular mechanics value of 2.3° outward.[95]

Methyl Rotations in Acetaldehyde, Acetone, Propene, 2-Methylpropene, and *cis*-2-Butene. The calculated methyl rotational barriers for these molecules are presented in Table XVII. All of the barriers are in good agreement with experiment, except *cis*-2-butene. It is apparent from Table XVII that, except in *cis*-2-butene, the intrinsic torsional term dominates the barriers i.e., nonbonded effects are small. For this reason, and due to the fact that the methyl barriers vary widely among these molecules, it is not possible to obtain reasonable calculated barriers with a combination of nonbonded effects and a single, 1,4-independent X–C–CT–Y parameter, invariant for all X and Y. Examination of the 1,4 permutations seen in these molecules reveals five types of 1,4 torsion: T_1, HA—CT—C═O; T_2, HA—CT—C—H; T_3, HA—CT—C—CT: T_4, HA—CT—C═C; and T_5, HA—CT—C—HA. Two types occur per molecule; i.e., acetaldehyde has T_1 and T_2, acetone has T_1 and T_3, propene and *cis*-2-butene have T_4 and T_5, and 2-methylpropene has T_3 and T_4.

Fitting to the experimental barriers was performed by leaving the existing nonbonded parameters unchanged and by manually adjusting the torsional parameters. Parameterization of the 1,4-dependent torsional terms can be achieved by finding a solution to the set of five simultaneous linear equations, each of the form

Table XVIII. Parameterization of the Intrinsic Torsional Terms for Unsaturated Molecule Methyl Group Rotations[a]

atom types	rotational barrier	atom types	rotational barrier
HA—CT—C═O	0.582	HA—CT—C═C	1.998
HA—CT—C—H	0.624	HA—CT—C—HA	0.000
HA—CT—C—CT	0.120		

[a] The effective rotational barrier is given; i.e., the force constants as entered in Tables XIX–XXIV are multiplied by 6.

Table XIX. Atom Types

CT	tetrahedral (sp^3) carbon	C	planar (sp^2) carbon
HA	nonpolar hydrogen	O	carbonyl oxygen
H	polar hydrogen		

Table XX. Bond Length Parameters

		k_b (kcal/mol/Å)	b_0 (Å)
HA	CT	330.0	1.100
CT	CT	235.5	1.530
CT	C	187.0	1.524
C	O	595.0	1.215
C	H	330.0	1.110
HA	C	330.0	1.100
C	C	600.0	1.335

Table XXI. Bond Angle Parameters

			k_θ (kcal/mol/rad)^2	θ_0 (deg)
HA	CT	HA	37.79	108.5
HA	CT	CT	44.91	109.5
CT	CT	CT	60.0	113.0
CT	C	H	50.0	116.0
O	C	H	50.0	121.7
CT	C	CT	50.0	115.4
CT	C	O	64.6	122.3
HA	CT	C	55.3	109.5
CT	C	HA	50.0	114.0
HA	C	C	50.0	120.5
CT	C	C	50.0	125.5
HA	C	HA	50.0	118.0

Table XXII. Torsional Parameters[a]

				K_ϕ (kcal/mol)	n	δ (deg)
X	CT	CT	X	0.157	3	0.0
HA	CT	C	O	0.097	3	180.0
HA	CT	C	H	0.104	3	0.0
HA	CT	C	HA	0.000	3	0.0
HA	CT	C	CT	0.020	3	0.0
HA	CT	C	C	0.333	3	180.0

[a] Definition of torsional parameters: X refers to wild card specification; i.e., there is no 1,4 dependence in such torsions. The intrinsic torsional energy is evaluated separately for each of the torsion angles X-A-B-Y, making altogether nine torsional angles for an sp^3–sp^3 bond, and six for an sp^2–sp^3 bond. To find the contribution of a given torsional parameter to the intrinsic torsional barrier, the torsional force constant should be multiplied by twice the number of 1,4 interactions represented.

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Table XXIII. Improper Torsional Parameters

				k_w (kcal/mol/rad)^2	ω_0 (deg)
CT	H	C	O	20.0	180.0
CT	O	C	CT	20.0	180.0
CT	C	C	HA	20.0	180.0
HA	C	C	HA	20.0	0.0
C	C	HA	HA	20.0	180.0
CT	C	C	CT	20.0	180.0
C	C	HA	CT	20.0	180.0

Table XXIV. Lennard-Jones Parameters

	$E_{\min}$ (kcal/mol)	$r_{\min}/2$ (Å)
H	-0.0498	0.8
HA	-0.0045	1.468
C	-0.0903	1.8
CT	-0.0903	1.8
O	-0.1591	1.6

$\sum_{i=1}^{5} n_i T_i = A_n$, where A_n are the desired intrinsic torsional contributions to the experimental barriers of molecules 1–5 and n_i is 1 or 0 depending on whether T_i contributes to A_n. Each equation thus represents the contribution of each 1,4 torsional type, T_i, to the intrinsic torsional contribution A_n. As two of the types contribute to each molecule, n_i will be 1 for two T_i terms and 0 for the other three. For example, for acetaldehyde, the equation is simply $T_1 + T_2 = 1.19$ kcal/mol. For certain atom type assignments, this set of equations has no solution. For example, it can be shown that if the vinyl hydrogen were classed as polar, so that torsional types T_2 and T_5 were the same, the system of simultaneous linear equations would have zero determinant and would have no solution. The atom types used here do not lead to such a problem. In Table XVIII are presented the intrinsic barriers. The final 1,4 dependences employed in the current force field are given in Tables XIX–XXIV.

In acetaldehyde, the contribution from the rest of the relaxed potential energy acts against the intrinsic term to slightly reduce the net torsional barrier. This is in agreement with a previous calculation using an empirical force field,[109] where the out-of-phase van der Waals energy was computed to be 0.05 kcal/mol, in comparison to the present value of 0.09 kcal/mol. In propene, as in acetaldehyde, the nonbonded part of the rotational potential energy is out of phase with the intrinsic torsional part, causing a reduction in the barrier.

The experimental acetone barrier (0.78 kcal/mol) is considerably reduced compared to acetaldehyde (1.17 kcal/mol). In the previous calculation,[109] the van der Waals forces contribute 0.52 kcal/mol to the barrier. In our calculation, the nonbonded component is only 0.08 kcal/mol, out of a barrier of 0.77 kcal/mol, i.e., 10%. An inspection of Table XVII shows that the nonbonded contribution to the acetone barrier is ~0.07 kcal/mol greater than the nonbonded contribution to the acetaldehyde barrier, whereas the intrinsic torsional contribution is ~0.5 kcal/mol less. The nonbonded and intrinsic contributions to the 2-methylpropene barrier are both ~0.12 kcal/mol greater than in propene. These results indicate that, in the present force field, stabilization of the acetone transition state is represented by the intrinsic torsional terms rather than by 1,4 nonbonded interactions.

According to the assignment of 1,4 torsional dependences described above, the intrinsic contribution to the rotational barrier of *cis*-2-butene is required to be the same as that for propene, and thus the 60% experimental barrier reduction relative to propene seen in this molecule must be accounted for by nonbonded effects. Although, as expected, the calculated nonbonded repulsions at the energy minimum are considerable, and do decrease the barrier height, the magnitude of this decrease (0.45 kcal/mol) is insufficient to reduce the barrier height to a value within the experimental accuracy.

We now consider possible reasons for the discrepancy between the calculated and experimental *cis*-2-butene rotational barrier. One possible cause of error is the minimum energy geometry. An initial comparison of this, considering particularly the C—C=C angles and the close H···H distance, shows good agreement with previous results.[99,91,95] However, a closer look suggests that small changes of the structure can suffice to raise the energy minimum by several tenths of a kilocalorie per mole, and thus bring the results in accord with experiment. For example, the close H···H distance can be slightly reduced from the calculated energy minimum value of 2.04 Å to the previous value of 1.94 Å by a ~1° closing of the C—C=C angles, which would remain within the experimental range. As a result of this change, the close H···H interaction energy increases by 0.33 kcal/mol, due to a van der Waals increase of 0.26 kcal/mol and an electrostatic increase of 0.07 kcal/mol, and the overall methyl···methyl interaction energy increases by 0.38 kcal/mol, of which 0.37 kcal/mol is van der Waals and 0.01 kcal/mol electrostatic. These results suggest that small geometry changes, which are still in agreement with experiment, can produce increases in the van der Waals repulsions sufficient to produce large changes in the barrier height itself.

Alternatively, one can look at the effect of increasing the size of the hydrogen atom by altering the van der Waals parameters. With use of van der Waals parameters of $E_{\min} = 0.0020$ and $r_{\min}/2 = 1.8$, compared to the normal parameters of $E_{\min} = 0.0045$ and $r_{\min}/2 = 1.468$, the adiabatic barrier was reduced to 0.9 kcal, in reasonable agreement with experiment. These results suggest that the cause of the disagreement is at present undetermined, and a more accurate experimental minimum energy geometry would thus be useful.

V_2 Barriers of Acetone, 2-Methylpropene, and *cis*-2-Butene. The calculated acetone V_2 is larger than the V_1 barrier (0.78 kcal/mol), increasing to 0.935 kcal/mol, in comparison with previous calculations of 1.71 kcal/mol (0.92 kcal/mol V_1) using geometry-optimized 3-21G calculations[100] and 3.56 kcal/mol (0.75 kcal/mol V_1) (4-31G[100]). There is strong disagreement between these values for the V_2 torsion. The V_2 barrier for *cis*-2-butene calculated here is 0.4 kcal/mol greater than the V_1 barrier, in agreement with a previous calculation of 0.37 kcal/mol.[97]

4. Concluding Discussion

In this paper, an all-atom force field has been examined by using conformational calculations on several hydrocarbon molecules. A relatively simple functional form is used because the ultimate goal is to apply it to macromolecules of biological interest. We have focused on data pertaining to conformational transitions and energetics. Further development of the potential function with respect to other types of data will be presented elsewhere.[4] We have paid special attention to understanding the interplay between the various interactions that are needed in the potential function to reproduce the available experimental and ab initio results. The study of conformational energetics emphasizes the terms in the potential function of most importance in biological applications; they are the torsional, van der Waals, and electrostatic energy contributions.

The results of the calculations demonstrate that the form of the potential function used is capable of reproducing most of the experimental and quantum mechanical values for the geometries and conformational energetics of the molecules studied to within their determined accuracy. The success of the model is such that even some subtle series effects (e.g., the bond angles in CH_3– and CH_2– groups in alkanes) are reproduced. This is true despite the simplicity of the potential function, which employs harmonic bond length and angle terms without 1,3 or higher order valence interactions.

Particular attention has been paid to the reproduction of energy changes as a function of rotation about single bonds. Such conformational properties are of considerable importance in biological phenomena. Several types of single bond torsions occurring in proteins have been studied in relevant small molecule fragments here. Rotational barriers of the simplest molecules of the series considered (e.g., ethane) are found to be dominated by

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the intrinsic term. Nonbonded interactions normally contribute only a small amount to barrier heights in these molecules. This is in accord with quantum mechanical calculations which suggest that, in simple alkanes, aldehydes, ketones, and alkenes, the source of the barrier is the overlap (exchange) repulsion between the CH bond orbitals.[35,38,39,110–112] The calculations suggest that rotational barriers in more complex molecules, such as butane and tri-*tert*-butylmethane do have significant intramolecular nonbonded contributions. In some cases, to reproduce experimental rotational barriers, it was necessary to introduce dependence of the intrinsic torsional terms on the first and fourth atoms defining the torsional angle, as well as on the second and third.

The determination of an optimal set of charges for general use in condensed-phase biomolecular simulations was not the aim and was beyond the scope of the paper. However, we have examined the sensitivity of the conformational properties examined to the method of representation of the intramolecular electrostatic interactions. These play an important role in the quantitative reproduction and simple interpretation of several conformational phenomena, and in some cases appear to be necessary for even qualitative accuracy. Despite the small size of the atomic partial charges in the alkanes, short-range electrostatic interactions contribute the major portion of the gauche–trans energy difference in *n*-butane, although their decomposition does not reveal a dominant pairwise interaction. Interestingly, the *n*-butane trans–gauche energy is not reproduced even qualitatively when the 1,4 electrostatic interactions are reduced by 50%. Truncation of the long-distance electrostatic interactions does not greatly modify the results presented here, as the interactions studied are short range.

Inaccuracies in the force field, and in molecular mechanics force fields in general, are expected when examining small geometric effects resulting from electronic rearrangements, such as methyl group asymmetry. The methyl tilt angle and associated CH bond length asymmetry have been proposed to originate from hyperconjugative interactions.[110] The methyl group tilting in the calculations presented here results from nonbonded effects and is generally in qualitative agreement with previous estimates although the changes are usually too small. The CH bond length asymmetry results are in qualitative disagreement with the data.

For the type of force field that is used here, the bond length and angle force constants play a small role in determining the conformational effects under study. An accurate determination of these parameters, with the inclusion of Urey–Bradley terms, is being made by comparisons with the vibrational frequencies of small molecules.[4] Also we have not addressed the problem of intermolecular interactions in condensed phases. Comparisons of water interactions with polar groups are being made to optimize the nonbonded parameters. From the available results, it appears that only small modifications are required for the analysis used here to remain valid.

Deviations from experimental geometries and energies reported in this paper are small and not systematic in any obvious way that could be related to the form of the nonbonded functions. Nevertheless, in view of the importance of nonbonded functions for the macromolecular calculations for which the potential function is particularly suited, possible improvements in their formulation are being considered. For example, the nonbonded interactions included here are pairwise additive and isotropic. The inclusion of short-range polarization effects may prove useful, and at long ranges, efficient representations of the Coulombic electrostatic interactions are needed.[113]

The force field results presented here are being integrated with those from other work in progress and with parallel studies on amino acid fragments and peptides to produce an improved force field for application to protein simulations.

Acknowledgment. We thank Neena Summers, Martin Field, Anton Beyer, Setsuko Nakagawa, Don Bashford, Hong Guo, and Mark Whitener for useful discussions. The work was supported in part by a grant from the National Science Foundation.

Registry No. CH_3CH_3, 74-84-0; $CH_3CH_2CH_3$, 74-98-6; $CH_3(CH_2)_2CH_3$, 106-97-8; CH(*t*-Bu)$_3$, 35660-96-9; CH_3CHO, 75-07-0; CH_3COCH_3, 67-64-1; $CH_3CH{=}CH_2$, 115-07-1; $CH_3C(CH_3){=}CH_2$, 115-11-7; (*Z*)-$CH_3CH{=}CHCH_3$, 590-18-1; cyclohexane, 110-82-7.

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(117) Use of tables: To identify an internal coordinate specified in the tables, the atom labels in the drawings of the molecules (e.g., Figure 1) can be used. In cases where symmetry obviously results in several internal coordinates having the same values (e.g., the C–H bond lengths in ethane), only one of these is listed. Broken brackets indicate quantities averaged over all such terms. Experimental uncertainties, where known, are listed in brackets. All energies are in kilocalories per mole, all distances in angstroms, and all bond angles and torsional angles in degrees.