Molecular Mechanics (MM3) Calculations on Lithium Amide Compounds

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Abstract: The MM3 force field has been extended to deal with the lithium amide molecules that are widely used as efficient catalysts for stereoselective asymmetric synthesis. The MM3 force field parameters have been determined on the basis of the ab initio MP2/6-31G* and/or DFT (B3LYP/6-31G*, B3-PW91/6-31G*) geometry optimization calculations. To evaluate the electronic interactions specific to the lithium amides derived from the diamine molecules properly, the Lewis bonding potential term for the interaction between the lithium atom and the nonbonded adjacent electronegative atom such as nitrogen was introduced into the MM3 force field. The bond dipoles were evaluated correctly from the electronic charges on the atoms calculated by fitting to the electrostatic potential at points selected. The MM3 results on the molecular structures, conformational energies, and vibrational spectra show good agreement with those from the quantum mechanical calculations.

Introduction

Organolithium compounds are widely used as catalysts for stereoselective asymmetric synthesis. Asami has applied various chiral lithium amides that were prepared from (S)-proline to the transformation of epoxides to allylic alcohols,1 and has shown that several optically active allylic alcohols are obtained efficiently from cyclic and acyclic symmetrical epoxides with high enantioselectivity.2 (Scheme 1).

High enantioselectivity is supposed to come from the specific structure and the resulting stabilization energy of the reaction intermediate complex formed between the chiral lithium amide and the substrate. Several structural studies on lithium amides in solution and in the solid-state have been carried out by using 6Li and 15N-NMR,3 X-ray,4 and computational methods.5 Their structural study reveals that lithium amide molecules exist as oligomers with chelated structures, and the solvent molecules are often incorporated into these complexed oligomeric structures. Therefore, it is rather complex and difficult to predict the structure and energy of the reaction intermediate complex formed between the chiral lithium amide and the substrate during the course of the asymmetric synthesis. Not only measurement of the NMR spectrum of the lithium amide in solution, but also a computational approach may be necessary to evaluate the plausible intermediate complex structure of the lithium amide. Considering the size of the reaction intermediate complex and the actual CPU time necessary for calculation, we could think that molecular mechanics may be the most practical of the various computational approaches. The MM3 force field6 has been developed to reproduce an accuracy and reliability comparable to high level ab initio calculations including electron correlation, and/or elaborate experiments. If we can evaluate the inter- and intramolecular interactions that will occur in the lithium amide complex correctly with the MM3 force field, the structures and the conformational energies of related lithium amide complexes may be predicted appropriately with reasonable CPU time. At present, the MM3 force field can deal not only with hydrocarbons and polar organic molecules, but also with organometallic molecules (metallocenes).7 For a description of the metal-ligand interactions (π-bonding) in metallocenes, a very strong but otherwise ordinary (Hill type) van der Waals potential is used. As deduced from the case of the metallocene force field, we suppose that some specific interaction energy term is necessary to describe the interactions between the electropositive Li atom and the nearby electronegative atoms in the lithium amide complex. To study the


Key words: MM3; molecular mechanics; lithium amide; Lewis bonding potential; asymmetric synthesis
specific interactions inherent in the lithium amide molecules, MP2/6-31G* level ab initio calculations were carried out on simple lithium amide model compounds.

In this article we report the MM3 force field for the lithium amide on the basis of the structural studies carried out by MP2/6-31G* level quantum mechanical calculations. After determining a lithium amide MM3 force field, we are aiming to apply it to the theoretical design of efficient chiral lithium amide catalysts for more efficient stereoselective asymmetric synthesis.

The MM3 Force Field

Structural parameters such as natural bond lengths, bond angles, and force constant parameters for the MM3 force field must be determined first. Natural bond lengths and bond angles relevant to the lithium amides have been determined on the basis of the ab initio geometries of the model lithium amide molecules. As the model compounds, lithium methylamide (A), lithium ethylamide (B), lithium dimethylamide (C), lithium ethylenediamine (D), lithium propylamide (E), lithium pyrrolidine (F), and N-lithioethylenediamine (G) were chosen for ab initio calculations. The structures of the stable conformers of these model compounds were optimized by MP2/6-31G* calculations. The quantum mechanical (QM) calculations were carried out using the Gaussian 94 Revision D.4 program. Vibrational corrections for bond lengths were included to evaluate the bond lengths (\( r^{10} \)) in the MM3 force field from the ab initio determined approximate \( r_e \) value. The torsional potentials (V1, V2, V3) were estimated by fitting to the torsion potential curves drawn by the relevant dihedral angle driving (e.g., Li—N—C—C, Li—N—C—H) QM calculations (MP2/6-31G*, B3LYP/6-31G*) with 15 degree angle intervals.

Electronic properties inherent in the lithium amide molecules have to be examined carefully to develop an appropriate force field that enables the prediction of structures and conformational energies of the lithium amides correctly. As the lithium atom is very electropositive, not only the electronic effect of the positive charge on the lithium atom, but also the effect of the induced electronic charges generated on the neighboring atoms, should be adequately taken into account by MM3 parameters. We have decided that these electronic properties inherent in the lithium amide should be incorporated into the bond dipole (Li—N) and the Lewis bonding potential energy function. In our previous report on MM3 studies of substituted triptycenes, we have proposed that the Lewis bonding interaction term should be added into the MM3 force field in the case where an electrophilic atom (E) is located intra- and/or intermolecularly close to a nucleophilic atom (Y) (Fig. 1).

Lewis bonding can be understood as being similar in nature to hydrogen bonding. The origin of the interaction can be thought as coming in part from a dipole–dipole interaction and in part from the donation of electrons by a donor atom (having a lone pair electrons such as oxygen and nitrogen) into the \( \sigma^* \) orbital of the E—X bond (E: electrophilic atom, X: electronegative atom). Considering the similarity between Lewis bonding and hydrogen bonding, a similar (but without angular term) potential function as for the hydrogen bonding interaction in the MM3 force field was used for the Lewis bonding interaction [eqs. (1) and (2)]. Only the constants are expected to differ in the two cases.\(^{12}\)

If \( P < 3.02 \)

\[
E_{\text{LB}} = (\varepsilon_{\text{LB}}/D)(1.84 \times 10^6 \exp(-12.0/P) - 2.25P^0) \quad (1)
\]

If \( P > 3.02 \)

\[
E_{\text{LB}} = (\varepsilon_{\text{LB}}/D)(192.270P^2 + 1706.96) \quad (2)
\]

The Lewis bonding energy parameter \( \varepsilon_{\text{LB}} \) (kcal/mol) and the equilibrium Lewis bonding distance parameter \( r_{\text{LB}} \) (\( \text{Å} \)) in eqs. (1) and (2) were determined specifically for the case of the lithium amides. The interaction energy for the Lewis bonding pair atoms (e.g., Li···N in the case of the \( N \)-lithioethylenediamine) was evaluated from the model calculation (NH\(_3\)···LiNH\(_2\)). The basis set superposition error (BSSE) correction\(^{13}\) was carried out by the counterpoise method to estimate the energy \( \{ \text{E(NH}_3\text{···LiNH}_2) \} \) of the supramolecule (\( \text{NH}_3\text{···LiNH}_2 \)). The optimized Li···N non-bonded distance for this supra molecule was taken as an equilibrium Lewis bonding distance \( r_{\text{LB}} \) for the Li···N pair. The Lewis bonding interaction energy for Li···N pair \( \{ E_{\text{LB}}(\text{Li···N}) \} \) was derived from the eq. 3.

\[
\text{Potential function is expressed as in equations 1 and 2. Where}
\]

\( \varepsilon_{\text{LB}} = \text{Lewis bonding energy parameter in kcal/mol} \)

\( D = \text{Dielectric constant in MM3 force field} \)

\( P = \varepsilon_{\text{LB}} / R \)

\( r_{\text{LB}} = \text{Equilibrium Lewis bonding distance (Å)} \)

\( R = \text{Distance of the Lewis bonding pair. X··E} \quad \text{---} \quad Y (\text{Å}) \)

\( \theta = \text{Angle of: Y --- X··E} \)

\( l = \text{Bond Length of X··E (Å)} \)

\( l_0 = \text{Equilibrium bond length of X··E (Å)} \)

**Figure 1.** Lewis bonding model in MM3 force field.
\[ E_{LB}(\text{Li} \cdots \text{N}) = E(\text{NH}_2 \cdots \text{LiNH}_2) - E(\text{NH}_3) - E(\text{LiNH}_2) \] (3)

To reproduce the thus obtained \(E_{LB}(\text{Li} \cdots \text{N})\) value, a Lewis bonding energy parameter (\(e_{LB}\)) for the \(\text{Li} \cdots \text{N}\) interaction was determined so as to fit the potential function expressed by eq. (1). The same procedure was used to determine the \(e_{LB}\) and \(r_{LB}\) for other Lewis bonding pairs that are assumed to exist in the systems for the asymmetric synthesis experiments using lithium amides (e.g., a \(\text{Li} \cdot \cdot \cdot \text{O}\) Lewis bonding interaction is plausible between the lithium and the oxygen of tetrahydronafuran used as a solvent). Several possible conformations for the supramolecules of the Lewis bonding pair systems were investigated to evaluate the \(e_{LB}\) and \(r_{LB}\) values correctly.

The bond dipoles in the lithium amides were derived from the electronic charges on the significant atoms, and the corresponding bond lengths were obtained by MP2/6-31G* calculations. The electronic charge was obtained by fitting to the electrostatic potential at points selected according to the CHelpG scheme.\(^9\) The \textit{ab initio} bond length \(r_e\) was converted to \(r_g\) by taking into account the vibrational correction.\(^9\)

As the lithium atom type had not as yet been assigned in the MM3 force field, the new atom type for \(\text{Li}\) was introduced and assigned as number 163. The van der Waals parameters (\(r;\) van der Waals radius, \(e;\) hardness of atom) were originally set to be \(r_{Li} = 2.55\) Å and \(e_{Li} = 0.007\) kcal/mol, respectively. However, this original van der Waals radius seemed not to be appropriate to reproduce the structure of sterically congested lithium amide molecules such as \(\text{N}-\text{Li}-\text{ethylenediamine}\) (\(\text{G}\)) in MM3 calculations. Nonbonded van der Waals repulsive interaction energies between the lithium atom and its adjacent atoms became too large, due to the rather big van der Waals radius of the \(\text{Li}\). To overcome this problem, the van der Waals radius of lithium was reduced by 15%.\(^{15}\) As MP2/6-31G* level quantum mechanical calculations have shown that a significant amount of the electron density from the lithium atom in the lithium amide moves to the electronegative nitrogen atom, it is reasonable to assume a reduction of the van der Waals radius of the lithium atom in lithium amide. Therefore, the 15% reduced value (\(r_{Li} = 2.17\) Å) was specifically used as a plausible van der Waals radius of the \(\text{Li}\) for the lithium amide molecule.

In addition, a new atom type 164 (\(N^*\)) was also introduced for the nitrogen atom bonded directly to the lithium atom, because the electronic properties of the nitrogen atom next to the lithium atom were evaluated to be different from those of the amine nitrogen atom (atom type 8) by \textit{ab initio} calculations. A point to be considered for the lithium amide nitrogen atom (\(N^*;\) atom type number 164) is whether it should be treated as sp\(^3\) type \(N\) (atom type 8) or as sp\(^2\) type \(N\) (atom type 9). As quantum mechanical (QM) calculations have shown that the lithium amide nitrogen atom tends to take a planar structure, we decided to treat \(N^*\) as an sp\(^2\) nitrogen atom. It was thus necessary to add out-of-plane bending parameters for the \(N^*\) atom to the MM3 parameter list. Although a different atom type number was assigned to the lithium amide nitrogen atom (\(N^*\)), the same van der Waals parameter values (\(r\) and \(e\)) as assigned to the atom type 9 nitrogen atom were used for the newly assigned atom type 164 (\(N^*\)).

**Results and Discussion**

**The Structural Study of Lithium Amide Model Compounds by MP2/6-31G* Calculations**

The stable optimized structures and their conformational energies for lithium amide molecules were initially necessary as basic data for the development of the MM3 force field. MP2/6-31G* geometry optimization calculations on the seven lithium amide model compounds (\(\text{A} \sim \text{G}\)) showed their unusual structures were attributable to the polar lithium amide functional group. The results were summarized in Figure 2. The Li—N bond lengths for the lithium amides except for \(\text{G}\) were in the range of 1.768–1.788 Å, while for (\(\text{G-I}\)), the Li—N bond was elongated (1.799 Å). The N—H bond length was found to have an almost constant value ranging from 1.018 to 1.022 Å. This value is as the almost the same as the usual N—H bond length of an amine. The stretched Li—N bond length of the \(\text{N}-\text{Li}-\text{ethylenediamine}\) appears to be due to the intramolecular interaction between the \(\text{Li}\) and the nonbonded neighboring electronegative nitrogen atom. The bond angles of the Li—N—H and Li—N—C took significantly different values ranging from 120° to 140° and 120° to 132°, respectively, even in the simple lithium amides (\(\text{A} \sim \text{F}\)) where no special intramolecular interaction seems to exist. This fact suggests that the bond angles of the lithium amide group (Li—N—X; \(X = \text{H}, \text{C}\)) can be deformed easily by steric repulsion between the alkyl substituents attached on the nitrogen atom and the lithium atom. Easy deformation of the Li—N—X angles may be due to the weak covalent bond character of the Li—N bond. It is noteworthy that more drastic changes in the Li—N—H and Li—N—C angles occurred in the \(\text{N}-\text{Li}-\text{ethylenediamine}\) (\(\text{G}\)), even though the nitrogen atom is a common central atom for forming each bond angle. These angles were 140.3° and 109.5°, respectively (Fig. 2). These large angle changes may also come from the intramolecular Li···N interaction.

With regard to the conformations, lithium amide molecules showed a peculiar structure in which they prefer an eclipsed conformation with regard to the rotation around the bond between the lithium amide nitrogen (\(N\)) and the \(\alpha\)-carbon atom (\(\text{C}_{\alpha}\)) next to the nitrogen. The nitrogen atom of the lithium amide group took on an almost planar structure. It is interesting that the simple lithium amides (\(\text{A} \sim \text{D}\)), where atoms and/or alkyl groups attached to the nitrogen atom are less bulky groups such as hydrogen, methyl, and ethyl substituents, preferred to take on the eclipsed conformation for the Li—N—C\(_{\alpha}—\text{H}\) and Li—N—C\(_{\alpha}—\text{C}\) dihedral angles. On the contrary, one of the most stable conformations of lithium propylamide (\(\text{E-4}\)) was more staggered form (\(\omega = 24°\)) with respect to the rotation around the N—C\(_{\alpha}\) bond, to relieve the steric repulsion among the substituents that would occur in the eclipsed conformation. The dihedral angle of Li—N—C—C in the most stable conformer (\(\text{E-I}\)) was 114°, which also corresponds to the deformed eclipsed conformation.

Although there existed a stable eclipsed conformer (\(\text{E-3} : \omega(\text{Li—N—C}_{\alpha}—\text{C}) = 0°\)) which is essentially as stable as (\(\text{E-I}\)) (\(\Delta E = +0.06\) kcal/mol), the deformed eclipsed (more staggered) forms (\(\text{E-I}\), \(\text{E-2}\), and \(\text{E-4}\)) were more dominant conformations than the eclipsed one in the lithium propylamide. In the case of the \(\text{N}-\text{Li}-\text{ethylenediamine}\) (\(\text{G}\)), the Li—N—C\(_{\alpha}—\text{C}\) dihedral
Figure 2. Geometries and conformational energies of the lithium amide model compounds calculated by MP2/6-31G* and MM3 (in parentheses).
angle was distorted a little bit from that of the eclipsed conformation (α(Li—N=Cα—C) = 25.3°). This unique dihedral angle of N-lithioethylenediamine (G) seems to arise from the balance between the attractive intramolecular Li—N Lewis bonding interaction and the steric repulsion among the substituents. To reach a favorable conformation for an attractive Li—N interaction, the dihedral angle (Li—N—Cα—C) should be 0° (eclipsed conformation) and then the dihedral angle (N—Cα—C—N) would move so that the other end amino nitrogen also wants the five-membered ring that is formed to have the ring bonds as staggered as possible (analogous to cyclopentanone). As a result, the two dihedral angles of α(Li—N=Cα—C) and α(N—Cα—C—N) in the most stable conformer (G-1) adjusted themselves to be −25.3° and 51.0°, respectively. This “Lewis bonding” favorable conformation was more stable by 19.4 kcal/mol than the second most stable extended anticonformer (G-2). This large energy stabilization of the quasi-gauche conformer over the anti indicates a strong Lewis bonding attractive interaction.

**Characteristic Properties of the Lewis Bonding Interaction Found in the Lithium Amide Model Compounds by MP2/6-31G* Calculations**

A rather large attractive Lewis bonding interaction seems to come from the electronic interaction between the electropositive lithium atom with the electronegative nitrogen atom. It should be clarified as to what extent the electronic charges are localized on each atom in lithium amide (Li—NH₂). In Table 1, the electronic charges on each atom evaluated by MP2/6-31G* calculations with the CHelpG scheme are shown. The electropositive lithium atom possessed +0.89 e charge, and the nitrogen atom next to it had rather large −1.84 e charge, which was partly compensated by the attached two hydrogen atoms. Judging from the large positive charge on the lithium atom, a rather strong attractive interaction is supposed to occur in the N-lithioethylenediamine (G). In fact, the distance and the overlap population between the Li and the N atoms support the attractive interaction. The stretched Li—N bond length (1.799 Å) and the shorter nonbonded Li—N distance (2.052 Å), and overlap population values between the Li and the two nitrogen atoms indicates that there exists an attractive interaction between the Li and the neighboring nitrogen atom (Table 1).

**Vibrational Spectra of the Lithium Amides Calculated by MP2/6-31G***

To identify the frequencies characteristic of the Li—N stretching and bending vibrational modes by *ab initio* calculations, vibrational analysis was carried out on lithium methylamide (A) and on lithium ethylamide (B) by the MP2/6-31G* calculations with a single overall scaling factor (0.95). For comparison, a B3-PWP91/6-31G* calculation using the selective optimized scale factors suggested by Pulay10 was also carried out on lithium methylamide (A). The two sets of frequencies for lithium methylamide were almost the same. Furthermore, we have carried out the MP2/6-311++G(2d, 2p) vibrational analysis on lithium amide (LiNH₂) and lithium methylamide (A) to make sure the accuracy and the reliability for estimating the frequencies of the vibrational modes inherent in the lithium amide functional group by QM calculations.

**Evaluation of the Lewis Bonding Energy by MP2/6-31G* Calculations**

The calculated frequencies for lithium methylamide (A) by the sophisticated MP2/6-311++G(2d, 2p) calculations with a single overall scaling factor (0.95) did not show any significant difference from those obtained by MP2/6-31G* calculations. Therefore, we judge that MP2/6-31G* level calculations can predict adequately the frequencies of the lithium amides. The calculated frequencies and the vibrational modes by single overall scaling MP2/6-31G* are shown in Table 2. The characteristic Li—N stretching vibrational mode was predicted to occur at 725 cm⁻¹ for both lithium methylamide (A) and lithium ethylamide (B) by the MP2/6-31G* calculations. In the wave number region lower than Li—N stretching mode, the frequencies that are mixed in with other vibrations were observed. As shown in Table 2, those frequencies correspond to those coupled with various motions of atoms connected to lithium atom, such as bending, out-of-plane bending, torsion, scissoring, etc. We are now in the process of determining the experimental IR spectrum of the synthesized lithium amide, to compare the experimental frequencies with those calculated by MM3 and QM methods.
The Li atom was placed in the direction favorable for interaction with the lone-pair electron orbital on the ammonium nitrogen atom, and the geometry was optimized by MP2/6-31G* calculations. The correction of the Basis Set Superposition Error (BSSE) was carried out by the counterpoise method.

The evaluated Lewis bonding energy between Li and N (E_{LB(Li... N)}) was 20.5 kcal/mol. The Lewis bonding energies obtained and the nonbonded interactive distances relevant to the Lewis bonding are summarized in Table 3. These two derived interaction energies for Li...O Lewis bonding (almost the same energies) indicate that E_{LB(Li... O)} energy is primarily determined by the intrinsic nature of the interacting atoms (Li and O). It is plausible to assign unique Lewis bonding energy parameters for the specific atom pairs such as Li...N and Li...O in the MM3 force field.

Table 3. The Lewis Bonding Energies and Structures for Model Systems by MP2/6-31G* Calculations.

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*Diff: Wave number difference (MM3 - MP2/6-31G*).

The LiNH₂—NH₃ model system as shown in Table 3. The Li atom was placed in the direction favorable for interaction with the lone-pair electron orbital on the ammonium nitrogen atom, and the geometry was optimized by MP2/6-31G* calculations. The correction of the Basis Set Superposition Error (BSSE) was carried out by the counterpoise method.

The evaluated Lewis bonding energy between Li and N (E_{LB(Li... N)}) was −20.5 kcal/mol. The equilibrium distance between Li and N was 2.100 Å. The Lewis bonding energy for the Li...O case was also evaluated with the same method in cases of Li—NH₂...ethylene oxide and Li—NH₂...dimethyl ether. The Lewis bonding energies obtained between Li and O were −17.6 and −17.8 kcal/mol, respectively. The Lewis bonding energies obtained and the nonbonded interactive distances relevant to the Lewis bonding are summarized in Table 3. These two derived interaction energies for Li...O Lewis bonding (almost the same energies) indicate that E_{LB(Li... O)} energy is primarily determined by the intrinsic nature of the interacting atoms (Li and O). It is plausible to assign unique Lewis bonding energy parameters for the specific atom pairs such as Li...N and Li...O in the MM3 force field.
**MM3 Calculations on Lithium Amide Compounds**

The new MM3 parameters for lithium amide compounds are listed in Table 4, the selected compared results of the MP2 and MM3 conformational energies and geometries are summarized in Figure 2, and the MP2 and MM3 vibrational frequencies are shown in Table 2. With regard to the geometries, MM3 does reproduce the structures specific to the lithium amides. The Li—N bond length and the relevant bond angles to the lithium amide functional group could be evaluated well on the whole. By using the reduced van der Waals radius for the lithium atom, we could predict the structures and the conformational energies correctly, even for conformers where there seems to occur an attractive interaction between the lithium atom and the proximately located electronegative nitrogen atom, such as (G-1). If we used the original van der Waals radius value ($r_{vdw} = 2.55 \text{ Å}$) for the lithium atom, MM3 calculations showed a rather big deviation (+0.036 Å larger) from the MP2/6-31G* calculations with regard to the nonbonded Li—N distance (2.052 Å) in the (G-1) conformer, even though the Lewis bonding energy term was introduced into the MM3 force field. The MM3 calculations with the new optimized parameter set (Table 4) reduced this nonbonded Li···N distance from 2.088 to 2.069 Å. However, the enlarged Li—N bond length due to the Lewis bonding interaction in (G-I) could not be reproduced completely. The Li—N bond length (1.780 Å) calculated by MM3 is still too short by 0.019 Å, and any improvement could not be recognized by reducing the van der Waals radius of Li by 15%. At present, the nonbonded Li—N distance and enlarged Li—N bond length in the (G-I) conformer are major structural problems in the MM3 force field for these compounds. It is very difficult to evaluate the change of the bond length properly in the current MM3 force field due to the rather big electron delocalization on an ionic polar bond such as Li—N. To reflect the electron delocalization effect on the ionic polar bond length precisely, further special treatment might be necessary for the Li—N bonds with the MM3 force field. The situation could be improved using a stretch–stretch interaction between the C—N bonds, but such a term is not part the MM3 force field.

The other point to be noticed with regard to the geometry is the wide change of the bond angle for Li—N—X (X = H, or C) in the model lithium molecules (A–G). For example, Li—N—C, Li—N—H, and H—N—C in conformer (G-I) are 109.5°, 140.3°, and 109.1°, respectively (Fig. 2). This bond angle Li—N—H of 140.3° is mysterious (G-1). The fact is that it changes a lot from one. The force constant is practically zero, and different compounds have this angle varying over an extremely wide range. By assigning rather small MM3 bending force constants for these bond angles in the lithium amides, MM3 could reproduce these big bond angle changes well. The determined MM3 bending constants ($k_\theta$) for Li—N—C and Li—N—H bond angles are 0.050 and 0.050 (mdyne Å/rad²), respectively. These smaller bending force constants enable easy deformation of the Li—N—C and Li—N—H bond angles, and lead to the larger bond angle changes to relieve the steric repulsion among the substituent groups around the lithium amide moiety. However, we may have to consider

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<td>164-1-5</td>
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<td>0.000</td>
<td>0.007</td>
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</table>

$^a$Five-membered ring.
$^b$Hardness of atom.
$^c$van der Waals radius of atom.
$^d$Lewis bonding energy parameter in kcal/mol.
$^e$Distance of the Lewis bonding pair.
$^f$Lone-pair electrons are located on atom X.
$^g$Number of lone pairs on atom X.
Figure 3. The structure and the frequencies of lithium methylamide (A) calculated by MP2/6-31G* and MM3 (in parentheses).

Further how to deal with the lithium nitrogen atom ($N^*$: atom type 164) properly in the MM3 force field, because it seems to be rather strange that the Li—N—H angle in the (G-1) conformer has such a large value ($140.3^\circ$). If the lithium amide nitrogen atom (atom type 164) uses sp$^2$ hybridized orbitals to form the covalent bonds, the three relevant bond angles (Li—N—H, Li—N—C, and H—N—C) would be expected to have similar values. Why does the Li—N—H bond angle become so much larger ($140.3^\circ$) than the other two angles ($109.1^\circ$ and $109.5^\circ$)? We have no completely satisfactory explanation to describe the chemical bonds comprising the lithium amide functional group. It might be not appropriate to treat lithium amide nitrogen (atom type 164) sp$^2$ type nitrogen atom as a trigonal planar system, although the out-of-plane bending force constants for these three bond angles are necessary to hold the planarity of the lithium amide moiety and to reproduce the bending frequencies obtained by the QM calculations.

The conformational energies, and the preference for the eclipsed conformation around the N—Ca bond can be adjusted by using the torsional potentials, particularly V2 and V3, for the Li—N—C—H and Li—N—C—H sequences. The MM3 calculations reproduce the MP2/6-31G* calculations fairly well.

With regard to the frequencies of lithium methylamide (A), we could fit the MM3 frequencies to the MP2/6-31G* frequencies by taking the trans lone-pair effect into account (RMS = 39 cm$^{-1}$). Without this effect, the deviation of the MM3 frequencies from the MP2/6-31G* frequencies was rather large, especially for the C—H stretching vibrations and the H(4)—N(1)—Li(3)—C(2) out-of-plane bending mode vibrations. The largest difference was +195 cm$^{-1}$ for the frequency observed at 468 cm$^{-1}$ by the MP2/6-31G* calculation (Table 2). The trans lone-pair effect is sometimes called the Bohlmann effect, or negative hyperconjugation. A lone pair of electrons is donated into a vicinal $\sigma^*$ bonding orbital, and an antiperiplanar geometry is optimum for such donation. The result is that the presence of electrons in the $\sigma^*$ orbital causes the corresponding bond to stretch, and the bond becomes weaker and the stretching force constants smaller. In Figure 3, the calculated frequencies and the relevant C—H bond lengths by MP2/6-31G* were shown. We find, as expected, that the stretched C—H bonds [C(2)—H(5), C(2)—H(6)] have lower frequencies (weaker bond) than the C(2)—H(7) bond. The C(2)—H(7) bond whose stretching vibration was predicted to have a higher frequency (2964 cm$^{-1}$) than the other two C—H bonds was oriented so as to be eclipsed with the N(1)—Li(3) bond. Natural Bond Orbital (NBO)$^{19}$ analysis on the MP2/6-31G* results showed that the lone-pair orbital of the nitrogen atom was directed perpendicularly (up and down, both directions) to the plane formed by Li(3), N(1), and C(2) atoms. Thus the trans lone-pair effect cannot effectively occur with the C(2)—H(7) bond. Some delocalization of the lone-pair electrons into the $\sigma^*$ orbitals of the C(2)—H(5) and C(2)—H(6) bonds is possible in this conformation. Thus, the lower frequencies and slightly stretched bond lengths for the C(2)—H(5) and C(2)—H(6) bonds are consistent with the “trans lone-pair effect.” As the agreement of the MM3 frequencies with those obtained by MP2/6-31G* QM calculations are reasonable, the MM3 force field parameters for the lithium amide group appear to be adequate for the structural study of the lithium amide compounds.

From these MM3 results on the lithium amide above, we think the geometry and the conformational energies of the lithium amide are evaluated correctly on the whole, together with the vibrational spectra. The addition of the Lewis bonding energy term and the rather small bending force constant values are the noteworthy characteristics of the lithium amide MM3 force field. In the future we are going to apply this MM3 force field to the reaction intermediates for the asymmetric syntheses of allylic alcohols (Scheme 1) using the chiral lithium amides to try to find the proper structures for high enantioselectivity. It seems to worthwhile to try to design an effective chiral lithium amide catalyst for asymmetric syntheses by computational methods using this force field. Computational molecular design may enable organic chemists to more easily design systems for the purpose of carrying out asymmetric syntheses more smoothly and efficiently.

Acknowledgment

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References

12. The second equation ($P > 3.02$) is used to prevent two atoms from mathematically fusing when they get too close.
15. In the case where the center of the electron density of an atom does not coincide with the center of the mass due to the electron delocalization in the chemical bond (X—H bond: X = any nonhydrogen atom, for example), the reduction of the van der Waals radius of the corresponding atom is usually carried out in the MM3 force field. With regard to the van der Waals radius of lithium in the lithium amide, reduction by 15% was the best value to reproduce the calculated results done by the quantum mechanical methods.
pertain to functionalized molecules and will be addressed in separate publications.21

The Force Field

The force field derived will be presented first, and then the details of the derivation will follow. The equations that describe the force field are similar to those in MM2, but there are some differences.

Bond Stretching. The quadratic term is adequate to describe bond stretching in all but a few cases; for those, the addition of a cubic term is sufficient to take care of all of the structural calculations. However, it was noted with the early version of MM2 that the cubic term causes the energy function to turn over and go to minus infinity as the atoms separate. If one uses a fairly poor starting geometry, where bonds are stretched beyond the energy maximum, then the molecule flies apart. This was fixed in different ways in various versions of MM2, but clearly a better fix is to simply add a quartic term, so that the energy goes up to plus infinity rather than down to minus infinity. Thus, if the starting geometry is poor, one will still end up automatically at the proper place. Knowing the value for the quadratic and cubic constants, one can derive the quartic constant needed to best represent a Morse potential; that value was used22 in eq 1.

\[ E_i = 71.94k_d(l - l_0)^2[1 - 2.55(l - l_0) + (7/12)2.55(l - l_0)^2] \]

(1)

Angle Bending. When the aliphatic C–C–C bond is bent to a smaller angle, the quadratic approximation seems to be adequate for most cases. However, with four-membered rings, the bending is clearly too severe for the ordinary bending constant and a quadratic formulation, from the approximately tetrahedral angle, to be used. Since different parameters are needed for four-membered rings, one cannot use them to get information on the cubic bending constant for open chains. However, some information on this point is available from a comparison of cyclobutane with the compound bicyclo[1.1.1]pentane, where the secondary carbon has a bond angle of approximately \(74^\circ\).23 In the former the bending is sufficient to bring the cubic constant into play relative to cyclobutane. One would also like to fit the heat of formation of these compounds, and these pieces of information narrow considerably the range in which the cubic bending constant must lie. There is a problem here, because the key compound is highly strained, and therefore may not be well-described by the force field. Hence, while we might fit the experiment, the results may not really be as good as they look. And, in fact, there really is no experimental value for the heat of formation, but there is an ab initio value,24 which we take to be equivalent.

On the other hand, if a secondary bond angle is opened from the tetrahedral value to some much larger value, then we have some measure of the cubic constant on the other side of the deformation, and there are several compounds that are helpful here. We also used up to a sextic constant in our preliminary optimizations. The higher constants were used to obtain the best fit to the available data, but they are not very well determined. There was considered important that they yield a monotonic function up to 180° so that no artificial minima are introduced. The function arrived at is

\[ E_{\theta} = 0.021914(k_{\theta})(\theta - \theta_0)^2[1 - 0.014(\theta - \theta_0) + 5.6(10^{-5})(\theta - \theta_0)^2 - 7.0(10^{-7})(\theta - \theta_0)^3 + 9.0(10^{-10})(\theta - \theta_0)^4] \]

(2)

In MM2 we had used only the quadratic and the sixth power terms, the latter having been chosen to fit the geometry of bicyclo[1.1.1]pentane. While this equation fit the data available to us at that time, with more and better data now available it is clearly not the best formulation. In MM2, part of the reason for the low values of the bending constants seems to have stemmed from the fact that the cubic term was omitted, which would have had the same effect at large bendings in the angle opening direction. It is clear that the MM3 formulation is a better representation than that used in MM2 for both small and large bendings.

Torsion. As with MM2, we use a three-term Fourier series expansion (eq 3) to represent torsional energy, where the torsional

\[ E_\varphi = (V_1/2)(1 + \cos \omega) + (V_2/2)(1 - \cos 2\omega) + (V_3/2)(1 + \cos 3\omega) \]

(3)

angles are calculated between all pairs of atoms that have a 1–4 relationship. The importance of the \(V_1\) and \(V_2\) terms in eq 1 has been well documented.2,3

Stretch–Bend Interaction. As with MM2 and other force fields, this interaction (eq 4) has been used so as to allow bonds

\[ E_{\omega} = 2.51118K_{\omega}[(l - l_0)(1 + \cos 3\omega) \]

(4)

to stretch somewhat when the angle between them is reduced, and to shrink when that angle is increased, analogous to the effect of a Urey-Bradley term in that type of force field.25 This effect is similar in MM3 to what it was in MM2. The extra stretching needed in special cases has been brought about partly with the torsion–stretch interaction, and partly by the separate adjustment of the \(l_0\) values in four- and five-membered rings. As with MM2, this interaction is counted only when the bond being stretched and the angle being bent are centered at the same atom.

Torsion–Stretch Interaction. Bond lengths in MM2 did not stretch sufficiently upon eclipsing. Thus, for example, the 2–3 bond in norbornane, which is experimentally the longest bond in the molecule,19 was of only average length according to MM2. Many other examples have been discussed previously.12,13 With this torsion–stretch interaction (eq 5) added, a much better fit

\[ E_{\omega} = 11.995(K_{\omega}/2)(l - l_0)(1 + \cos 3\omega) \]

(5)

to molecular geometries when bonds are other than perfectly staggered is obtained.

It might be thought that the stretch–bend interaction can be used to take care of the 2–3 bond stretching in norbornane,25,26 but this is not the case. The 2–3 bond is definitely much longer in norbornane than the 1–7 bond, and if this stretching is brought about only with the aid of a stretch–bend interaction, the 1–7 bond length always stretches more than the 2–3 bond length does.

Torsion–Bend Interaction. This interaction has been used previously to bring about bending of cyclobutane rings.26 However, it also caused excessive bending in five-membered rings. We accordingly revised the interactions in MM2, in which case it turned out that the torsion–bend interaction was not needed, and is has been used in MM3. Actually, a small torsion–bend interaction might be desirable to reproduce certain observed features. In the ethane molecule, for example, the C–C bond does not stretch enough without the appropriate interaction terms, and the C–C–H angles do not open enough when the molecule eclipses. The C–C stretching has been taken into account with the torsion–stretch interaction, and the torsion–bend interaction could similarly account for the bending upon eclipsing. However, the effect is not very large,11 and we have decided to ignore it and have left out this interaction in MM3.

Bend–Bend Interactions. Spectroscopic studies3 indicate that bending vibrations which involve two angles centered on the same atom give calculated frequencies which are too close together if this type of interaction term is omitted. By including this interaction, these frequencies can be split apart to match better with

(22) The authors are indebted to Prof. L. S. Bartell for this value.
experimental vibrational spectra. We have chosen only generic type constants here, where the angles either involve two carbons (or other heavy atoms) attached to the central carbon, or one carbon and one hydrogen, or two hydrogens. The equation is as given by

\[ E_{\text{vdW}} = -0.021914K_{\text{vdW}}(\theta - \theta_0)(\theta' - \theta'_0) \]  

van der Waals' Interactions. At the time MM2 was developed, the closest approach between two hydrogens which has been experimentally measured accurately occurred in cyclodecane, and the distance between them was 1.942 Å (our estimated probable error in this value is 0.053 Å; see later under cyclodecane). MM2 fit this value marginally well, calculating 2.000 Å. More recently, three hydrocarbon structures have become available in which there are even closer approaches of hydrogen atoms. There is also one chlorinated hydrocarbon in which there is a still closer approach. The two most useful compounds for our purposes were studied by Ermer, by neutron diffraction at low temperatures, and hence the positions of the hydrogens relative to one another are quite accurately known. These two compounds have the structures I and II shown later. They are derivatives of exo,exo-tetracyclo-[6.2.1.1^3,6.0^7.7]dodecane. The distance between the closest hydrogens opposing each other on the one-carbon bridges are respectively 1.748 and 1.698 Å (probable errors 0.010 Å), whereas the MM2 values calculated are 1.890 and 1.837 Å, which are clearly much too large.

We decided in view of the above that a softer van der Waals' function would be desirable, and hence reduced the exponent in the MM2 formulation from 12.5 to 12.0, as:

\[ E_{\text{vdW}} = \frac{a}{2.25(r/r_0)^\alpha + 1.84(10)^3 \exp[-12.00(r/r_0^5)]} \]  

This formulation gives us only two adjustable parameters, the sum of the van der Waals' radii \((r_i)\), and the \(\alpha\) value, or energy parameter, for the interaction between two atoms. Because MM2 worked as well as it did, we know that the values there are close to being correct, and we started from that point. We noticed that the MM2 values gave heats of sublimation for normal alkanes which were too large. This indicated that we had either to make the van der Waals' radii or the \(\alpha\) values smaller for either the hydrogens or the carbons, or some combination. From studies on graphite, we were able to establish the proper parameters for aromatic carbon. We felt that the parameters for aliphatic carbon must be similar to aromatic carbon, but the aliphatic carbons need to be identical. We also wanted to fit the positions of the close hydrogens in compounds I and II acceptably well, and so we made some more minor adjustments in the van der Waals' parameters of carbon and hydrogen.

We recognized the above problem years ago, when Ermer's data on compounds I and II were published. We did not, however, feel that an ad hoc correction of the van der Waals' parameters in MM2 was desirable, because while they could have been changed (softened) in order to accomodate Ermer's data, every movement would have been to accommodate Ermer's data, everything else in the force field is dependent on those parameters. If they are changed, then one would really need to go back and optimize the whole force field again; that is to say, one would need to develop a completely new force field. Otherwise, the changes brought about in unexpected places by the van der Waals' changes may do more harm than good.

After the adjustments described, it was clear that we could fit the data for Ermer's compounds and still fit the cyclodecane structure as well as previously (in fact, somewhat better than with MM2), and in addition fit acceptably well (better than MM2) the crystal packing and heats of sublimation of a number of aliphatic hydrocarbons. We also fit to aromatic hydrocarbons at the same time, so that we could study compounds which contained both aromatic and aliphatic portions to make sure the balance was correct; studies on graphite have been previously mentioned.

We also examined the other two compounds which have very close hydrogens, namely, secododecahedrane (III), and the chlorinated birdcage compound (IV) studied by Ermer and Anet, which is a derivative of pentacyclo-[6.2.1.1^3,6.0^7.7]dodecane (V). These compounds are less useful for our purposes, the former because it was studied only by X-ray crystallography and the hydrogens were not accurately located, and the latter, which is somewhat beyond the scope of the present MM3 hydrocarbon work, because of the presence of the chlorines. The preliminary calculations that we carried out did indicate that reasonable structures for these compounds were obtained using MM3.

Electrostatics. We assumed with MM2 that a neutral molecule could have its charge distribution represented by a set of bond dipoles. Others have used point charges on atoms rather than point dipoles in bonds to represent molecular electrostatics, and from everything we know at this point, the two approximations are overall nearly equivalent. We have not seen any convincing information that indicates that one approximation is in general conspicuously better than that other. Accordingly, we have decided to use the same approximation in MM3. However, we do wish to study molecules which contain net charges, as in proteins, and hence we have added to the program the capability for calculating not only dipole–dipole and charge–charge interactions, but also charge–dipole interactions, which must be included in this approach. But for saturated hydrocarbons, as will be discussed here, these things are not pertinent.

Next comes the question: should we have bond dipoles for C–H bonds or for C–C bonds? It is certainly true that aliphatic hydrocarbons have quite small dipole moments, which can be taken as zero for our present purposes. But it is generally considered that the hydrogen has a small charge relative to a carbon. The definition of quantum mechanical charge is less than straightforward, however, and it is not clear that charges in alkanes are needed in molecular mechanics. Our philosophy is therefore as previously: namely, we will take those bond dipoles to be zero unless it is convincingly shown that a nonzero value must be used to obtain desired results. In the case of benzene, it is clear that one must have charges on the hydrogens and carbons if one is to reproduce the crystal structure, the stability of the perpendicular benzene dimer, and related facts. The magnitude of the C–H bond moment required here was not well determined but had to be equal to at least 0.6 D, above which value one obtains the qualitatively proper results. This is close to the value deduced independently by earlier workers and so has been incorporated into the MM3 program. But for aliphatic C–H bonds, we still see no evidence indicating that a nonzero dipole moment is necessary. Accordingly, we have assigned a zero bond moment to the aliphatic C–H bond. The aliphatic C–C bonds in purely aliphatic hydrocarbons do not have a dipole moment in the MM3 approximation. (Bond moments need not be zero between C epis–C epis, etc., and are not in MM2 and MM3). Strictly, the C epis–C epis bond could have a bond moment if the two carbons are not identical, one primary and one secondary, for example, but we assume such values can be taken as zero to an acceptable approximation.

Rotational Barriers. In principle, one only needs to fix values for the parameters \(V_1\), \(V_2\), and \(V_3\) for any given four atom linkage A–B–C–D, and then rotational barriers should be properly calculated. Note that one cannot simply transfer these constants from ab initio calculations, from spectroscopy, or from other places. One has to actually fit the experimental (or ab initio) potential curve, and the values for these constants required in molecular mechanics will not be the same as those given by the methods mentioned. The reason for this is that in molecular mechanics the van der Waals' energies also change as a function of the angular rotation, and one wants to match the total energy, not

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(30) We are indebted to Dr. J. Ponder for a copy of his subroutine for the charge–dipole interaction calculation.
(32) Charges are necessary if one wishes to calculate infrared intensities, but they are not needed in the present context, and the infrared problem will be dealt with separately.
just the part which is due to the torsional equation (eq 3).

The problem here is less than straightforward, however. In principle, one can fit the $H-C-C-H$ $V_2$ constant from the known ethane barrier, the $H-C-C-C$ constant from the neopentane barrier, and the $C-C-C-C$ constant from the butane barrier. The results may then be checked against experimental and ab initio barriers in other molecules, or one might use some kind of weighted procedure to determine the torsional parameters from a larger amount of data. There are several problems that have to be faced. In spectroscopic measurements, the formalism usually applied does not allow for the fact that the molecule is relaxing in other internal coordinates as the rotation occurs, and therefore the spectroscopic barrier is higher than the barrier that would be calculated by molecular mechanics. Barriers observed by some methods, such as NMR, are typically determined between vibrational levels, not between the equilibrium points at the botom and the top of the barrier, and this introduces some discrepancy. Trivially, but most importantly, one must be careful about comparing values for the enthalpy, which are usually calculated, with those for the free energy, which is often observed experimentally and which may be quite different.

Specifically, we have fit ethane on the low side (experimental barrier 2.88 kcal/mol, MM3 barrier 2.41 kcal/mol). We have to fit the barrier on the low side in order to obtain a reasonably accurate value for the torsional frequency, which is calculated with the harmonic approximation. If we calculate a larger value for the barrier, the torsional frequency will also become larger, as will quantities which depend upon this frequency, such as the enthalpy. For neopentane, we have also chosen to calculate a somewhat low value (3.35 kcal/mol versus 4.2-4.8 kcal/mol). The rotational barrier of butane has been a subject of much discussion, particularly the cis or $0^\circ$ barrier, relative to the trans conformation. The MM2 value for this barrier was 4.7 kcal/mol for $\Delta H_{298}$, in agreement with the experimental (spectroscopic) value$^{33}$ of 4.6 kcal/mol for $\Delta E$. More recent ab initio calculations have determined this energy as 5.8-6.0$^{34}$ or 6.3$^{35}$ kcal/mol for $\Delta H_{298}$, in apparently poor agreement with experiment. Our objective with MM3 is not to fit the butane value as accurately as possible, but rather to obtain a general parameter set which will fit alkane data in general as accurately as possible. These data include, in particular, the rotational barriers in congested molecules and the heats of formation of compounds which contain partly or completely eclipsed bonds, such as the twist-boat form of cyclohexane, medium-ring cycloalkanes, and bicyclo[2.2.2]octane. When the fitting is optimized over all of the available data which we have examined,$^{3,6}$ the MM3 value for the butane barrier obtained is 4.8 kcal/mol. There is some arbitrariness here, because the result obtained is dependent on the weighting scheme which is used and the particular data to which it is applied. If one chooses to weight different experiments in different ways, this value of 4.8 kcal/mol might reasonably be raised or lowered by 0.2 kcal/mol or possibly, at the outside, by 0.3 kcal/mol. However, it does not seem possible with any reasonable weighting to get a number which is very near the ab initio values (discrepancy $\sim 0.6$ to $-1.1$ kcal/mol). One must, of course, ask why. The reason now appears to be that the basis sets used by earlier workers were too small. With a larger basis (triple $\alpha$ + 2 sets of d functions on carbon, and p functions on hydrogen), the barrier calculated$^{36}$ is quite a bit lower, 5.22 kcal/mol for $\Delta H_{298}$, or 4.89 for $\Delta H_{298}$.

**Parametrization**

The above formulation gives our force field for aliphatic hydrocarbons. It was then necessary to determine the parameters that go into the force field. This was done beginning with the necessary bending and stretching parameters, taking them to be equal to the spectroscopic force constants, and then calculating

\begin{align*}
\text{(A) Bond Lengths and Stretching Parameters} & \\
\text{bond} & l_0 & K_s & \\
C-C & 1.5247 & 4.49 & \\
C-H & 1.112 & 4.74 & \\
\end{align*}

\begin{align*}
\text{(B) Angle Bending} & \\
\text{atom types} & \theta_1 & \theta_2 & \theta_3 & \\
C-C-C & 0.57 & 109.5 & 109.5 & 111.0 & \\
C-C-H & 0.59 & 109.8 & 109.3 & 110.7 & \\
H-C-C-H & 0.55 & 107.6 & 107.8 & 109.5 & \\
\end{align*}

\begin{align*}
\text{(C) Torsional Parameters} & \\
\text{atom types} & \psi_1 & \psi_2 & \psi_3 & \\
C-C-C-C & 0.192 & 0.230 & 109.9 & 111.0 & \\
\end{align*}

\begin{align*}
\text{(D) Stretch-Bend} & \\
\text{bond} & K_{sb} & \\
C-C-C & 0.13 & \\
C-C-H & 0.08 & \\
H-C-C & 0.00 & \\
\end{align*}

\begin{align*}
\text{(E) Torsion-Stretch} & \\
\text{bond} & K_{ts} & \\
C-C & 0.059 & \\
\end{align*}

\begin{align*}
\text{(F) Bend-Bend} & \\
\text{angle} & K_{bb} & \\
C-C-C & 0.24 & \\
C-C-H & 0.30 & \\
H-C-C & 0.00 & \\
\end{align*}

\begin{align*}
\text{(G) Van der Waals' Parameters} & \\
\text{element} & \text{atom type} & \epsilon & R_{VDW} & \text{at. wt} & \\
C & 1 & 0.027 & 2.04 & 12.000 & \\
H & 5 & 0.020 & 1.62 & 1.008 & \\
\end{align*}


$^{34}$ Raghavachari, K. J. Chem. Phys. 1984, 81, 1383.


$^{17}$ Cyclopropanes will be reported on separately.

$^{8}$ Bond lengths in Å, angles in degrees; stretching, bending, and torsion parameters are in mdyne/Å, mdyne Å/rad$^2$, and kcal/mol, respectively.

$^{9}$ There are three types of $\theta$, 1, 2, and 3, where the central atom of the atom considered is bound to zero, one, or two hydrogens (or deuteriums), respectively, apart from the atoms that make up the angle considered.

$^{10}$ The value of $K_{bb}$ in eq 5 is the product of the two constants $K_{sb}$ in the table as appropriate for the angles involved.

*many known structures to obtain values for $l_0$, $\theta_0$, etc. Having then good geometries for the molecules, the vibrational spectra were examined, and the force parameters were further adjusted so as to fit these within the limits discussed earlier.*