MM3(96) parameterization for camptothecin analogs:
An ab initio and molecular mechanics study

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Summary

Torsional parameters for MM3(96) were derived for the missing atom types present in the natural product camptothecin (CPT). Potential energy curves were calculated via ab initio calculations on representative compounds for dihedral angles containing these missing parameters. Gaussian 92 at the restricted Hartree–Fock level of theory using the standard 6-31G** and 4-31G** basis sets, was used for all the quantum-mechanics calculations. Missing MM3 torsional terms were obtained by optimizing the V_1, V_2 and V_3 parameters such that MM3 could reproduce the ab initio torsional profile. MM3 calculated molecular structures that compare well with the ab initio results. Using the newly developed parameters, conformational analyses and QSAR studies of camptothecin analogs were undertaken. MM3 predicts two distinct 'boatlike' conformations for the α-hydroxy lactone moiety. The low-energy lactone conformation predicted by MM3 is in general agreement with reported X-ray crystal structures of CPT iodoacetate and 7-ethyl-10-(4-piperidino)piperidinylcarbonyloxy CPT HCl as well as the ab initio structure of a CPT-like α-hydroxy lactone.

Introduction

Enantiomerically pure 20-(S)-camptothecin (Fig. 1) was first isolated from the wood and bark of *Camptotheca acuminata* [1] in 1966 by Wall and co-workers, and was later found in the bark, stem, and roots of *Mappia foetida* [2]. 20-(S)-Camptothecin, hereafter abbreviated as CPT, inhibits eukaryotic type I DNA topoisomerase and has been the lead compound for several analogs in clinical trials against a variety of cancers [3]. A large number of CPT derivatives have been synthesized and evaluated for topoisomerase I inhibition by a number of research groups [4–6]. In conjunction with QSAR studies, conformational analyses of these therapeutically useful compounds using the MM3 [7] molecular mechanics force field have been undertaken.

Molecular mechanics has become a standard and powerful tool for the analysis and prediction of molecular structure and related properties [8–10]. The molecular mechanics approach determines the energy of a molecular system in terms of Newtonian type forces between the nuclei and defines specific molecular 'atom types' based on the identity and hybridization state of the atoms. Molecular mechanics calculations are based on potential energy equations that require accurate parameters. The current MM3 force field equation is given by

$$E = \sum E_S + \sum E_B + \sum E_T + \sum E_{OOP} + \sum E_{vdW} + \sum E_{\mu\mu}$$
$$+ \sum E_{QQ} + \sum E_{SB} + \sum E_{BB} + \sum E_{TS} + \sum E_{Q\mu} \quad (1)$$

In this equation, the total energy (E) of a molecular system is the summation of the bond stretch (E_S), angle bend (E_B), torsion (E_T), out-of-plane bend (E_{OOP}), van der Waals (E_{vdW}), dipole–dipole ($E_{\mu\mu}$), and ion–ion (E_{QQ}) contributions. Also included in the force field are the important cross-terms defining the stretch–bend (E_{SB}), bend–bend (E_{BB}), torsion–stretch (E_{TS}) and ion–dipole ($E_{Q\mu}$) interactions. Several necessary torsional parameters for CPT were undefined in MM3 and had to be derived prior to an accurate conformational analysis. The torsional

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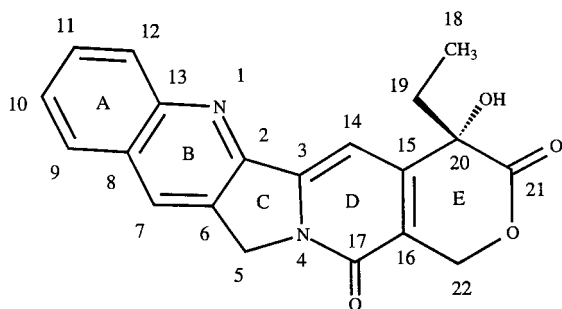
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Fig. 1. Chemical structure and numbering system for 20-(*S*)-campto-thecin.

contribution to the MM3 force field is significant and is given by the equation

$$E_T = \frac{V_1}{2}(1 + \cos \omega) + \frac{V_2}{2}(1 - \cos 2\omega)$$
$$+ \frac{V_3}{2}(1 + \cos 3\omega) \tag{2}$$

The MM3 torsional parameters consist of V_1, V_2, and V_3 terms (in units of kcal mol^{-1}), which are modified by the dihedral angle ω. The first-order torsional constant V_1 is associated with dipole–dipole interactions, and a positive V_1 generates an energy maximum at 0° and a minimum at 180°. The second-order torsional constant V_2 is associated with planarity of unsaturated systems and hyperconjugation in alkanes. A positive V_2 term produces energy minima at 0° and 180° and a maximum at 90°. The third-order torsional term V_3 can be considered as steric in nature. A positive V_3 destabilizes *eclipsed* forms and gives butane-like energy minima at 60° and 180° with maxima at 0° and 120°. The torsional parameters V_1, V_2, and V_3 can be varied to reproduce any desired torsional curve.

In conjugated systems, such as butadiene, the V_2 torsional parameters, read in from a parameter file or from the program, are modified according to the equation

$$V_2 = V_2^0 \, p_{ij} \, \beta_{ij} \tag{3}$$

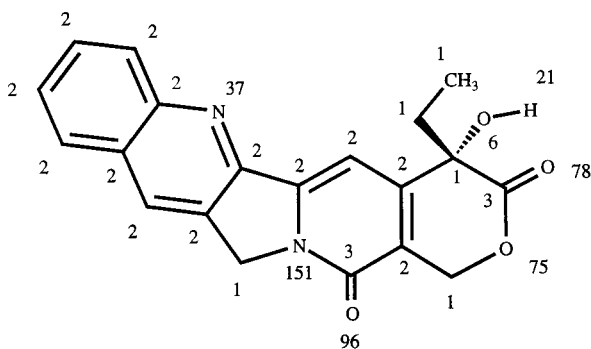where V_2^0 is the parameter read in from the parameter file

Fig. 2. MM3 atom types for CPT heavy atoms.

and V_2 represents the value used in the energy equation. As shown in Eq. 3, the V_2 parameter is modified by p_{ij}, the pi bond order of the two central atoms i and j, and by β_{ij}, the resonance integral for atoms i and j. The resonance integral β_{ij} is dependent upon the angle formed by the two p orbitals of the two central atoms i and j.

Heretofore, the application of the MM3 force field to CPT derivatives was limited due to the missing MM3 torsional and bending parameters. The MM3 atom types for CPT are shown in Fig. 2, and the missing MM3 parameters for this compound are summarized in Table 1.

Methods

Molecular mechanics force fields are increasingly utilizing ab initio calculations in the parameterization process. While MM3 is primarily parameterized to reproduce gas-phase electron diffraction data, ab initio calculations have been used effectively in the absence of experimental information. Therefore, the missing MM3 torsional parameters for the atom types present in CPT were derived from representative ab initio torsional curves.

The approach undertaken in developing the torsional parameters was to use, when possible, a molecule missing only the single torsional parameter of interest. A rotational energy profile was obtained by driving the defined torsion through 180° or 360°. At each point of the profile, the dihedral angle of interest was constrained while the remainder of the molecule was fully optimized. MM3 dihedral driver files were created using the optimized ab initio geometry. The MM3 torsional parameters V_1, V_2, and V_3 were optimized to reproduce the ab initio torsional profile by minimizing the standard deviation between the ab initio and the resulting MM3 relative energy curve.

Unless otherwise specified, ab initio calculations were carried out at the restricted Hartree–Fock level of theory with the standard 6-31G** basis set. Ab initio calculations

TABLE 1

MISSING MM3 TORSIONAL AND BENDING PARAMETERS FOR CPT

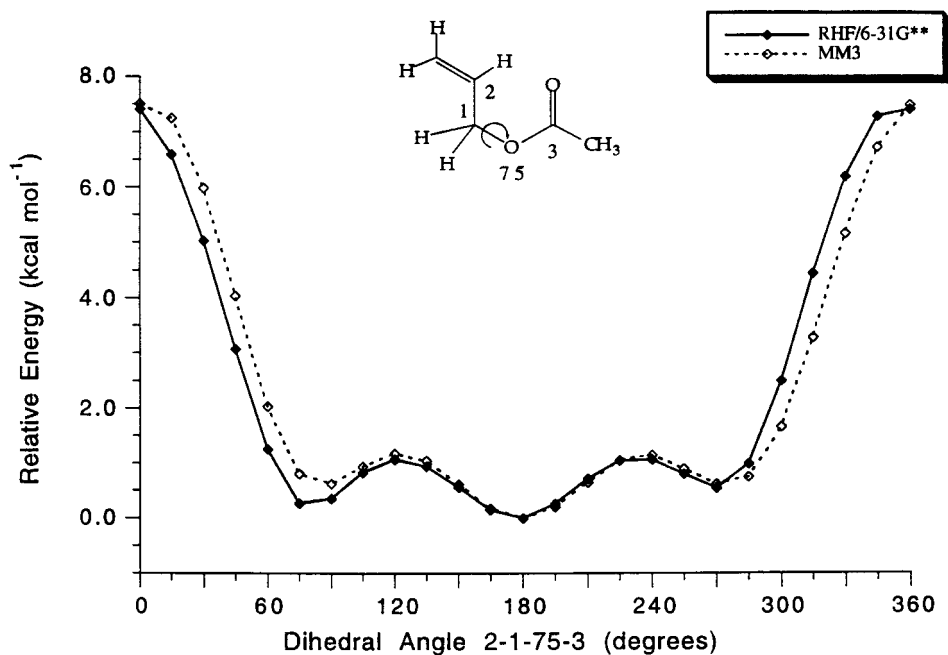| Entry	MM3 atom types	
Torsional parameters		
1	2-1-75-3	C_{sp2}-C_{sp3}-O_{sp3}-$C_{C=O}$
2	75-1-2-3	O_{sp3}-C_{sp3}-C_{sp2}-$C_{C=O}$
3	37-2-2-151	N_{pyr}-C_{sp2}-C_{sp2}-$N_{C=O}$
4	151-1-2-2	$N_{C=O}$-C_{sp3}-C_{sp2}-C_{sp2}
5	151-1-2-2	$N_{C=O}$-C_{sp3}-C_{sp2}-C_{sp2}
6	2-1-151-3	C_{sp2}-C_{sp3}-$N_{C=O}$-$C_{C=O}$
7	2-1-151-2	C_{sp2}-C_{sp3}-$N_{C=O}$-C_{sp2}
8	1-2-3-151	C_{sp3}-C_{sp2}-$C_{C=O}$-$N_{C=O}$
9	2-3-151-2	C_{sp2}-$C_{C=O}$-$N_{C=O}$-C_{sp2}
Bending parameter		
10	2-3-151	C_{sp2}-C_{sp3}-$N_{C=O}$

Fig. 3. Torsional profile of allyl acetate used for MM3 atom types 2-1-75-3.

were carried out using Gaussian 92 [11] on IBM RS/6000 workstations, and molecular geometries were analyzed using SYBYL 6.0 [12] on Silicon Graphics workstations. MM3 calculations were run using MM3(94) [13] on IBM RS/6000 and Silicon Graphics workstations. The newly derived parameters are incorporated into MM3(96).

For the parameterization of dihedral angles where the two central atoms are pi atoms, the MM3 FINAL ENERGY must be used for comparison with the ab initio data. While in nonconjugated systems the MM3 quan-

tities FINAL STERIC ENERGY and FINAL ENERGY are the same, in conjugated systems the FINAL ENERGY includes a calculation that modifies the FINAL STERIC ENERGY to the FINAL ENERGY, taking the delocalization of electrons into account.

Results

The first two of the missing parameters are for MM3 atom types 2-1-75-3 (C_{sp2}-C_{sp3}-O_{sp3}-$C_{C=O}$) and 75-1-2-3
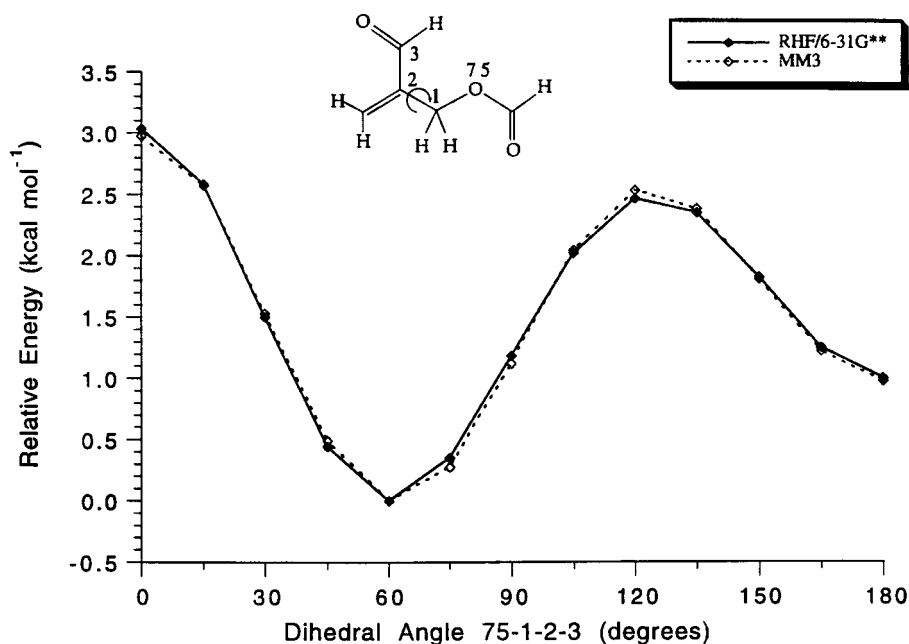

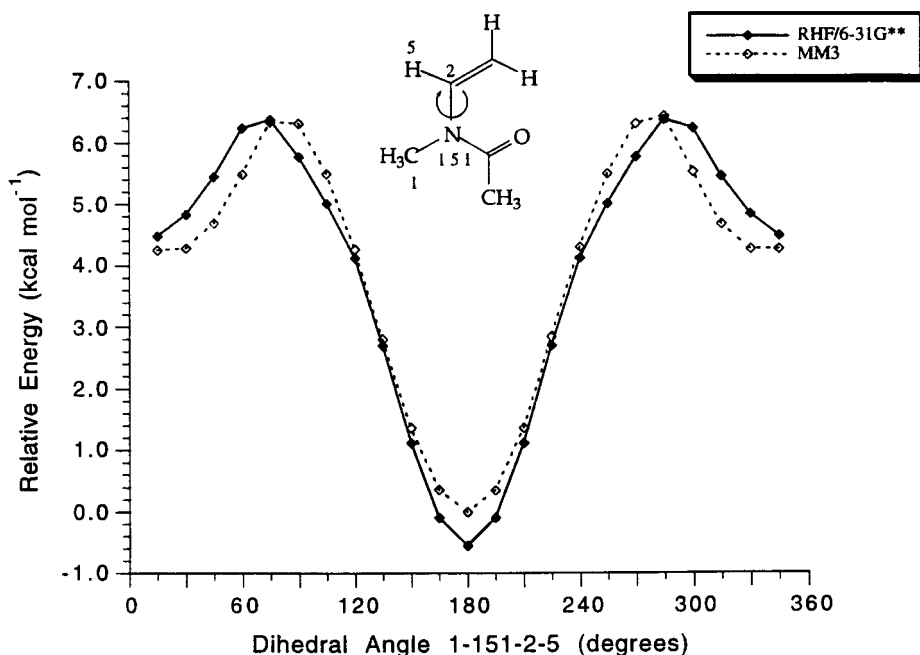Fig. 4. Torsional profile of 2-(formyloxymethylene)propenal used for MM3 atom types 75-1-2-3.

Fig. 5. Torsional profile of s-*cis*-*N*-methyl-*N*-vinyl acetamide used for MM3 atom types 1-151-2-5.

$(O_{sp3}\text{-}C_{sp3}\text{-}C_{sp2}\text{-}C_{C=O})$ and are shown in Table 1 and Fig. 2. These two torsional parameters are the most crucial for CPT, since they involve the flexible α-hydroxy lactone moiety essential for topoisomerase I inhibition and the antineoplastic activity of CPT. The 2-1-75-3 torsion was derived by using the allyl acetate ester shown in Fig. 3, as the representative compound, containing the critical dihedral angle.

With the 2-1-75-3 $(C_{sp2}\text{-}C_{sp3}\text{-}O_{sp3}\text{-}C_{C=O})$ parameters de-

rived, the 75-1-2-3 $(O_{sp3}\text{-}C_{sp3}\text{-}C_{sp2}\text{-}C_{C=O})$ torsional curve was obtained next, using 2-(formyloxymethylene)propenal as the representative compound. The structure and torsional profile are displayed in Fig. 4.

Several of the remaining parameters that needed to be determined involve MM3 atom type 151, which is a special amide type nitrogen. Currently in MM3, two atom types are reserved for amide type nitrogens. Atom type 79 is used for a regular amide nitrogen, and atom type 151
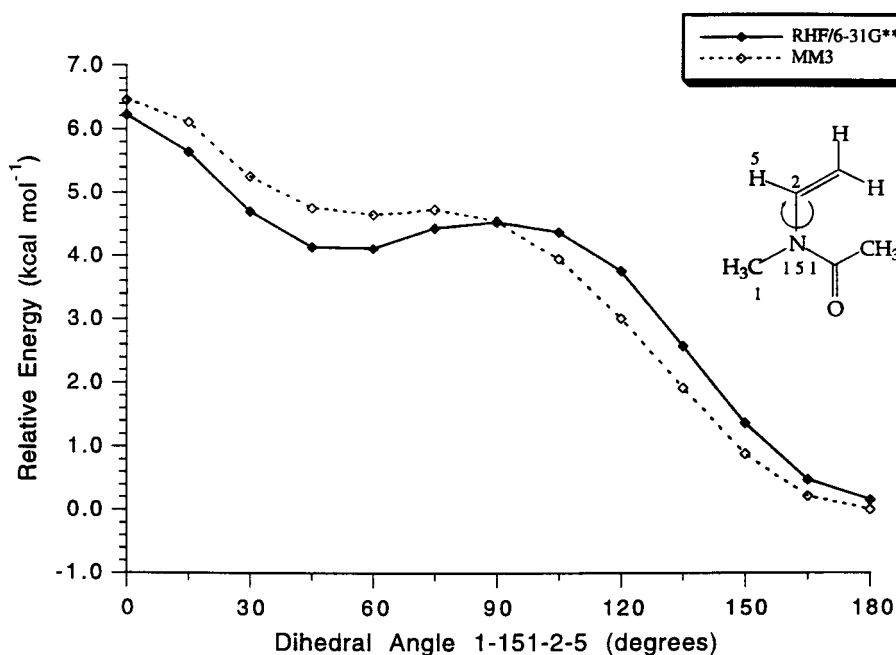

Fig. 6. Torsional profile of s-*trans*-*N*-methyl-*N*-vinyl acetamide used for MM3 atom types 1-151-2-5.
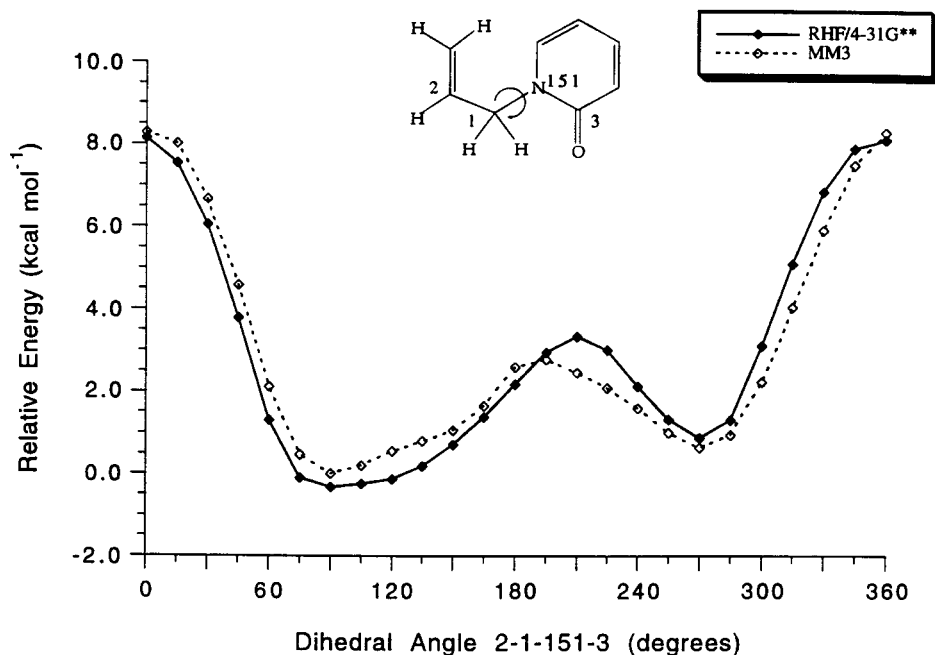
Fig. 7. Torsional profile of *N*-allyl pyridone used for MM3 atom types 2-1-151-3.

is reserved for an amide type nitrogen with the nitrogen adjacent to a carbon–carbon double bond. Thus atom type 151 defines an amide where the electrons on the nitrogen are further delocalized. Prior to obtaining the parameters for MM3 torsional angles 151-1-2-2 (N_{am}-C_{sp3}-C_{sp2}-C_{sp2}) and 2-1-151-3 (C_{sp2}-C_{sp3}-N_{am}-$C_{C=O}$), the parameters for 1-151-2-5 (C_{sp3}-N_{am}-C_{sp2}-H) were developed. Two torsional curves were used in defining the 1-151-2-5 parameters. Figures 5 and 6 show the two calculated torsional

curves for *N*-methyl-*N*-vinyl acetamide, which contains atom types 1-151-2-5. The torsional diagram for the s-*cis* conformation, in which the oxygen is cis to the ethylene group, is shown in Fig. 5, while the s-*trans* conformation, in which the oxygen is trans to the ethylene group, is shown in Fig. 6.

Although the s-*trans* structure, shown in Fig. 6, was found to be slightly lower in energy than the corresponding s-*cis* isomer, both torsional profiles were used for the
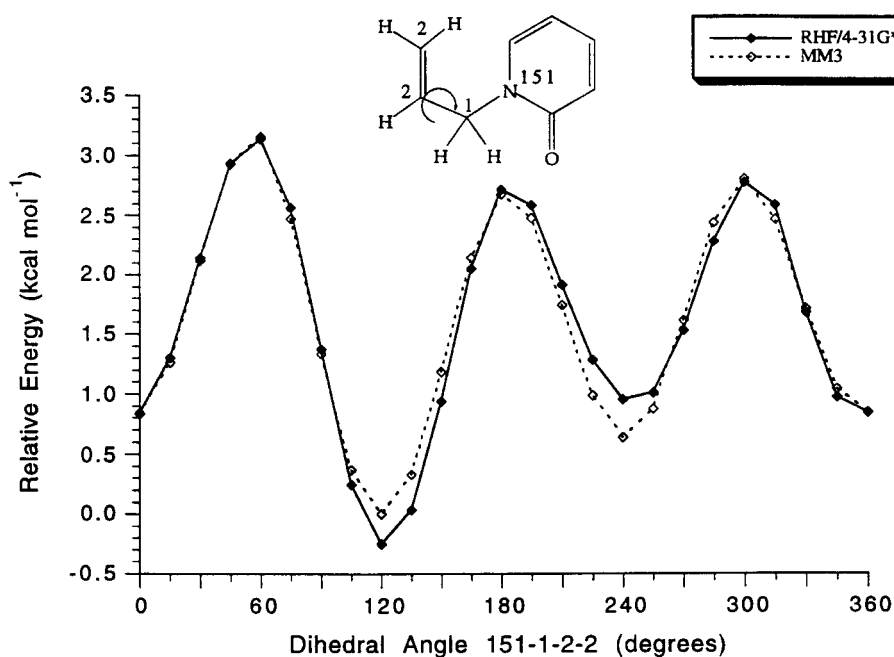

Fig. 8. Torsional profile of *N*-allyl pyridone used for MM3 atom types 151-1-2-2.
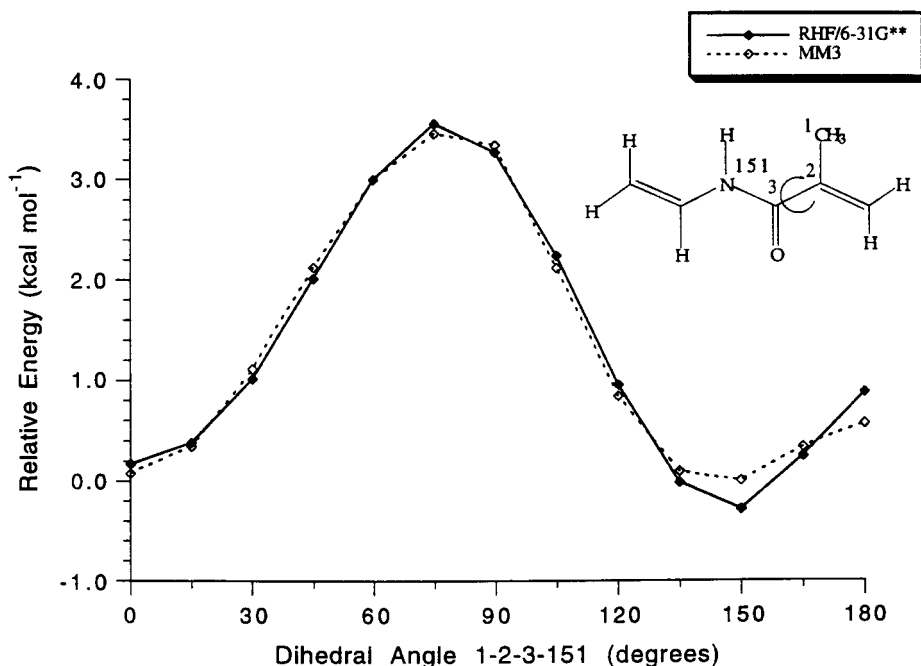
Fig. 9. Low-energy torsional profile of s-*cis*-*N*-vinyl-2-methyl propenamide used for MM3 atom types 1-2-3-151.

parameterization. In the course of deriving the 1-151-2-5 torsional parameters, it was initially difficult to reproduce the s-*cis* torsional profile. The problem lay in the 1-151-2-2 (C_{sp3}-N_{am}-C_{sp2}-C_{sp2}) torsion which is directly coupled to 1-151-2-5 (C_{sp3}-N_{am}-C_{sp2}-H). Originally in MM3, the 1-151-2-2 torsional parameters had been approximated with a V_1 of 0.0, a V_2 of 2.0, and a V_3 of 0.0. It was decided to optimize both the 1-151-2-5 and 1-151-2-2 parameters simultaneously, evenly dividing the value of V_2 between the two torsional terms.

With these parameters, torsional curves for 151-1-2-2 (N_{am}-C_{sp3}-C_{sp2}-C_{sp2}) and 2-1-151-3 (C_{sp2}-C_{sp3}-N_{am}-$C_{C=O}$) could be obtained. A combined approach using *N*-allyl pyridone was used, where this one molecule served as the basis for the two sets of parameters. Because these two torsional profiles took considerable CPU time, calculations were carried out using the RHF/4-31G** basis set. The first dihedral angle of the *N*-allyl pyridone which we studied focused on the 2-1-151-3 parameter shown in Fig. 7.
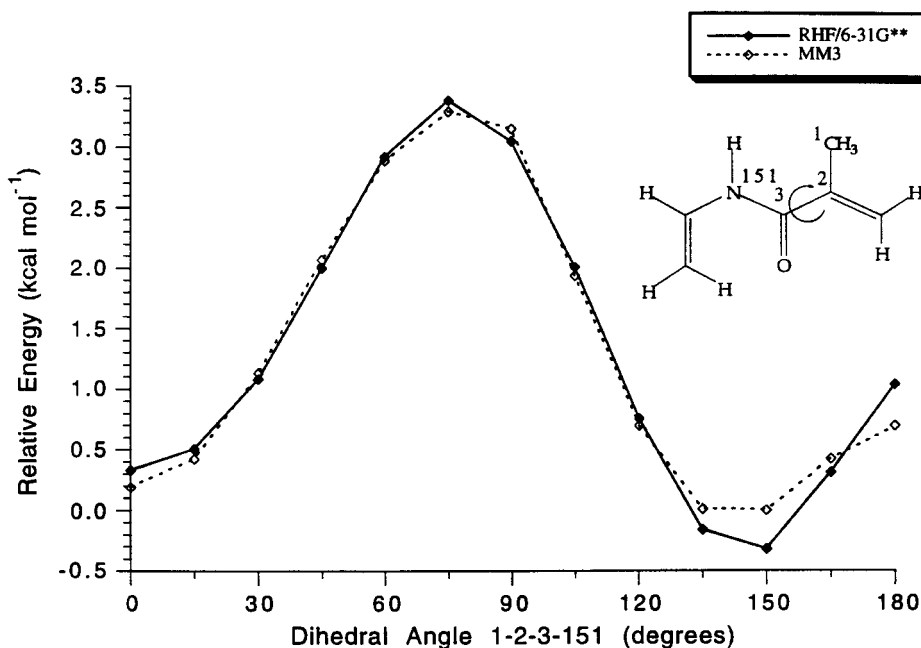

Fig. 10. High-energy torsional profile of s-*cis*-*N*-vinyl-2-methyl propenamide used for MM3 atom types 1-2-3-151.
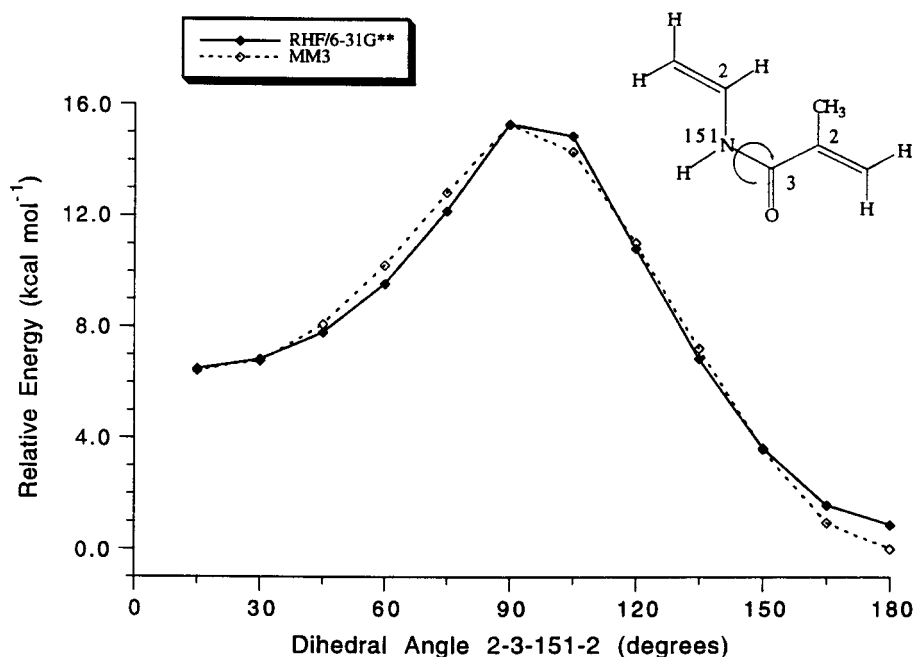
Fig. 11. Torsional profile of *N*-vinyl-2-methyl propenamide used for MM3 atom types 2-3-151-2.

The torsional parameters for MM3(94) types 2-1-151-2 (C_{sp2}-C_{sp3}-N_{am}-C_{sp2}), which is coupled to 2-1-151-3, had also been approximated and needed to be derived rigorously. Therefore, the torsional profile in Fig. 7 was used to optimize both 2-1-151-3 and the coupled 2-1-151-2 dihedral parameters. The resulting V_2 term, based on the ab initio profile, was evenly divided between 2-1-151-3 and 2-1-151-2. For these two dihedral angles, the two central atoms are not pi atoms, and the result is a rela-

tively small, negative V_2 contribution. As will be discussed later, in cases where the two central atoms are pi atom types, the result is a large positive V_2 contribution.

For the 2-1-151-3 and 151-1-2-2 torsional analyses, the ab initio and MM3 geometries were compared to ensure that the structures were at the same local minimum and had similar conformations. The second set of torsional parameters derived using the *N*-allyl pyridone are those for MM3 atom types 151-1-2-2, shown in Fig. 8.
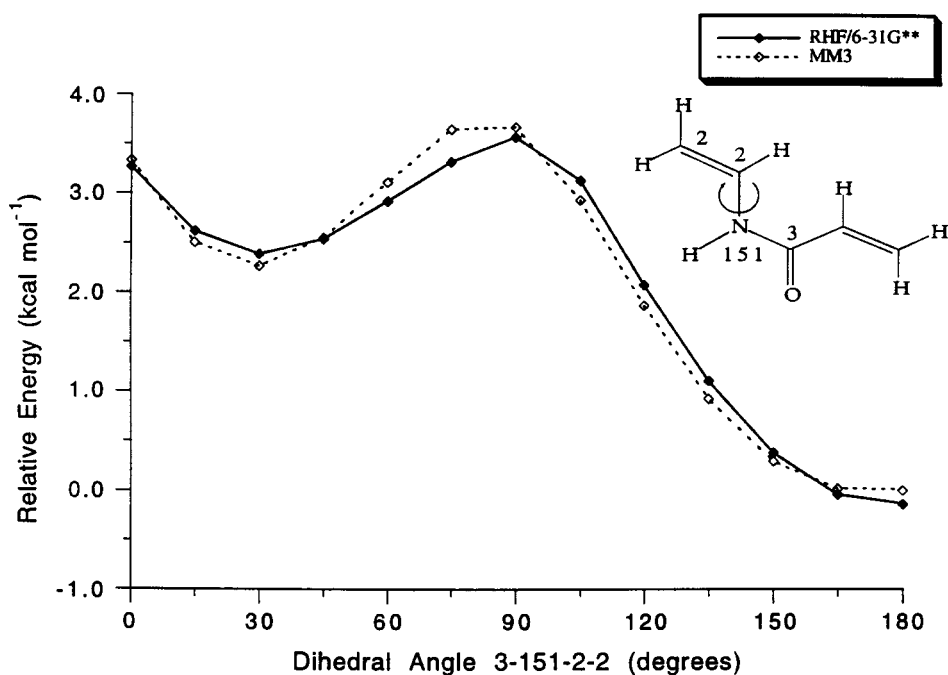

Fig. 12. Torsional profile of *N*-vinyl propenamide used for MM3 atom types 3-151-2-2.
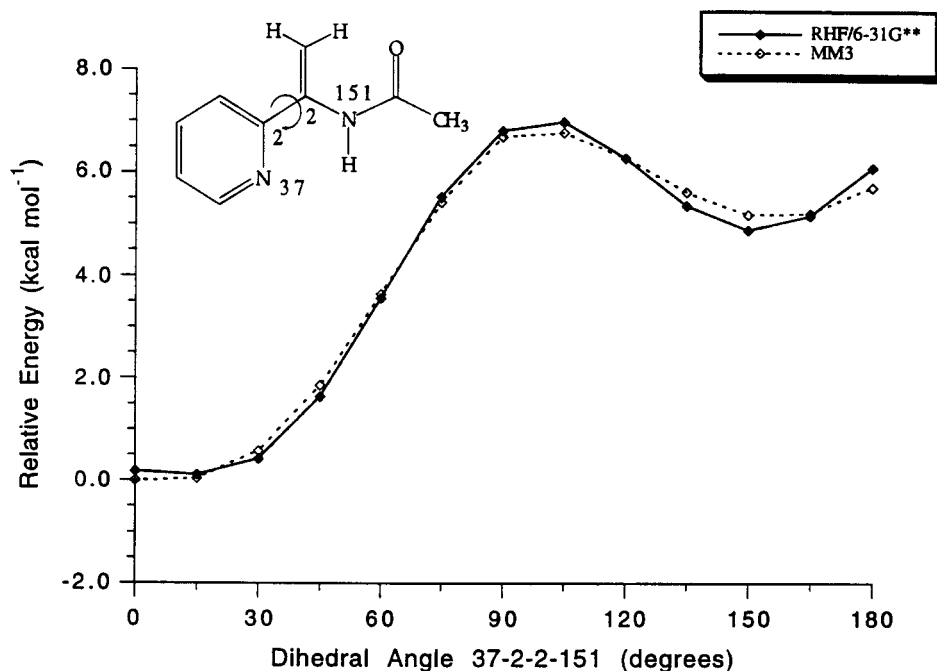
Fig. 13. Torsional profile of 2-(1-acetaminoethenyl)pyridine used for MM3 atom types 37-2-2-151.

In an analogous fashion to that described above for dividing the V_2 parameter between 2-1-151-3 and 2-1-151-2, the torsional parameters for 151-1-2-2 (N_{am}-C_{sp3}-C_{sp2}-C_{sp2}) and 151-1-2-5 (N_{am}-C_{sp3}-C_{sp2}-H) were optimized simultaneously. The V_2 parameter was evenly divided using the potential energy profile in Fig. 8. The total V_2 contribution was, in effect, split between the 151-1-2-2 and 151-1-2-5 torsions.

TABLE 2
FINAL CPT RELATED PARAMETERS

|	V_1 (kcal mol^{-1})	V_2 (kcal mol^{-1})	V_3 (kcal mol^{-1})	k_b (mdyn Å rad^{-2})	θ_0 (°)
Torsional					
2-1-75-3	0.7246	−0.6033	0.2583		
75-1-2-3	−0.7242	−0.9105	0.4165		
37-2-2-151	0.2390	11.9450	0.1420		
2-2-2-151	0.0000	11.9450	0.0000		
1-151-2-5	1.7980	5.0969	0.8890		
1-151-2-2	0.0000	5.0969	0.0000		
2-1-151-3	2.3160	−1.2460	2.1020		
2-1-151-2	0.0000	−1.2460	0.1000		
151-1-2-2	−0.3280	0.0150	−1.1990		
151-1-2-5	0.0000	0.0150	0.1000		
1-2-3-151	3.8040	9.1390	−1.1990		
2-2-3-151	0.0000	9.1390	0.0000		
5-2-3-151	0.0000	9.1390	0.0000		
2-3-151-2	−0.8350	11.0530	1.4310		
2-3-151-28	0.0000	11.0530	0.0000		
96-3-151-2	−0.6000	11.0530	0.0000		
96-3-151-28	1.0000	11.0530	0.0000		
79-3-151-1	−0.6000	11.0530	0.0000		
79-3-151-2	−0.6000	11.0530	0.0000		
79-3-151-28	1.0000	11.0530	0.0000		
2-2-151-3	0.0000	3.8570	−0.6310		
5-2-151-3	0.0000	3.8570	0.0000		
2-2-151-28	0.0000	3.8570	0.0000		
5-2-151-28	0.0000	3.8570	0.0000		
Bending					
2-3-151				0.695	120.0
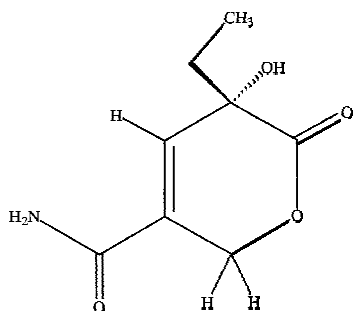
Fig. 14. 5-Carboxamide-3-ethyl-3-hydroxy-3,6-dihydro-2-pyrone used for the ab initio analysis of the CPT-like lactone.

Fig. 15. X-ray (bold) and MM3 calculated bond distances for low-energy CPT conformation.

It was also necessary to simultaneously optimize the 1-2-3-151 (C_{sp3}-C_{sp2}-$C_{C=O}$-N_{am}) and 2-3-151-2 (C_{sp2}-$C_{C=O}$-N_{am}-C_{sp2}) parameters. s-*cis*-*N*-Vinyl-2-methyl propenamide was used for the parameterization. Both the *N-cis* and *N-trans* structures for 1-2-3-151 were examined. The *N-cis* and *N-trans* notation applied here refers to the relative orientation of the *N*-ethylene moiety. The low-energy torsional curve in which the *N*-ethylene moiety is trans to the carbonyl group is presented in Fig. 9, while the higher energy torsional curve in which the *N*-ethylene moiety is cis to the carbonyl group is presented in Fig. 10.

The resultant V_2 term that best fit the 1-2-3-151 torsional profile was divided between 1-2-3-151 (C_{sp3}-C_{sp2}-$C_{C=O}$-N_{am}) and 2-2-3-151 (C_{sp2}-C_{sp2}-$C_{C=O}$-N_{am}). The V_2 contribution of 9.139 kcal mol^{-1} was also used for the V_2 of 5-2-3-151.

The torsional curve for MM3 types 2-3-151-2 was obtained using s-*trans*-*N*-vinyl-2-methyl propenamide and is shown in Fig. 11.

In this case, the V_2 term was split between the four torsions 2-3-151-2 (C_{sp2}-$C_{C=O}$-N_{am}-C_{sp2}), 2-3-151-28 (C_{sp2}-$C_{C=O}$-N_{am}-H_{am}), 96-3-151-2 (O_{sp2}-$C_{C=O}$-N_{am}-C_{sp2}), and 96-3-

151-28 (O_{sp2}-$C_{C=O}$-N_{am}-H_{am}). The V_2 parameters of the aforementioned four torsions were simultaneously optimized. In the course of this investigation, it was found that the 3-151-2-2 ($C_{C=O}$-N_{am}-C_{sp2}-C_{sp2}) and 3-151-2-5 ($C_{C=O}$-N_{am}-C_{sp2}-H) parameters had been approximated. The compound s-*trans*-*N*-vinyl propenamide was used to derive the 3-151-2-2 and 3-151-2-5 torsional parameters. The torsional curve for this is shown in Fig. 12.

Finally, 2-(1-acetaminoethenyl)pyridine was used for MM3 types 37-2-2-151 (N_{pyr}-C_{sp2}-C_{sp2}-N_{am}). Calculations carried out at the RHF/6-31G** level of theory are shown in Fig. 13. The torsional profile was obtained using both the 4-31G** and 6-31G** basis sets, but since the difference between the two ab initio curves was small, only the 6-31G** results are presented. The V_2 parameter for the torsional curve of Fig. 13 was split between 37-2-2-151 and 2-2-2-151 (C_{sp2}-C_{sp2}-C_{sp2}-N_{am}). The parameters for 37-2-2-151 were optimized with the V_2 contribution to the MM3 profile evenly divided between 37-2-2-151 and 2-2-2-151.

The complete list of all MM3 torsional parameters derived herein is displayed in Table 2. All torsional parameters in Table 2 were obtained using the ab initio data. The angle bending parameters for MM3 atom types 2-3-151 (C_{sp2}-$C_{C=O}$-N_{am}) use the automatically approximated MM3 parameter estimater [14] values of 0.695 mdyn Å rad^{-2} for k_b and 120.0° for θ_0.

Using these newly derived CPT parameters, a conformational analysis of the α-hydroxy lactone of CPT was undertaken [15]. It was found that low-energy conformers for the *S*-isomer of CPT had structures in which the lactone carbonyl was found on the same side of the CPT plane as the hydroxyl group at C20. *S*-isomers which had the carbonyl on the 20-ethyl side of the CPT plane were found to be several kcal mol^{-1} higher in energy.

Discussion

Although MM3 has primarily relied upon gas-phase and electron diffraction data, parameterization may also utilize high-level ab initio calculations when experimental data are unavailable, or not of sufficient accuracy to be

TABLE 3

TORSION ANGLES (°) FOR X-RAY, AB INITIO, AND MM3 MINIMIZED STRUCTURES

Torsion (lactone atoms)	X-ray		RHF/6-31G** [c]	MM3[d]
	1968[a]	1991[b]		
C16-C15-C20-C21	39.4	22.7	30.7	34.5
C15-C20-C21-O_{sp3}	−36.6	−27.3	−35.8	−31.8
C15-C20-C21-O_{sp2}	147.0	161.8	146.1	145.9
C20-C21-O-C22	−2.1	12.2	9.8	−6.1
C15-C16-C22-O_{sp3}	−33.3	−13.6	−27.4	−36.5
C16-C22-O_{sp3}-C21	36.0	8.3	22.3	39.9
C16-C15-C20-$O_{hydroxy}$	159.1	138.3	148.8	152.5
C16-C15-C20-C19	−86.9	−111.7	−89.1	−90.2
C15-C20-C19-C18	179.2	69.3	−60.5	−58.3

[a] X-ray structure of CPT iodoacetate [16].
[b] X-ray structure of 7-ethyl-10-(4-piperidino)piperidinylcarbonyloxy CPT hydrochloride trihydrate [17].
[c] From the ab initio calculations of lactone at RHF/6-31G** (Fig. 14).
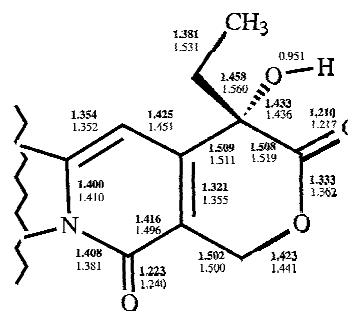[d] Global MM3 minima using derived parameters.

useful. Because of the relatively large number of heavy atoms in these representative structures, calculations were limited to the Hartree–Fock level of theory. Electron-correlated methods, such as found at the MP2 level of theory, are considerably more computationally intensive than Hartree–Fock methods. While electron-correlated methods result in a decrease in the IR frequency error, the effect on torsional profiles is not clear.

The MM3 low-energy structure for the CPT lactone was found to be in agreement with the X-ray structures of CPT iodoacetate [16] and 7-ethyl-10-(4-piperidino)-piperidinylcarbonyloxy CPT HCl [17]. In addition to the X-ray structures, MM3 results were compared to ab initio calculations on 5-carboxamide-3-ethyl-3-hydroxy-3,6-di-hydro-2-pyrone. This CPT-like unsaturated α-hydroxy lactone is shown in Fig. 14. The MM3 global minimum was used as a starting point for the ab initio optimization which was carried out at the RHF/6-31G** level of theory. The lactone torsional angles for the two X-ray structures, the ab initio, and the MM3 structures are presented in Table 3.

The X-ray and MM3 calculated bond distances are presented in Fig. 15. X-ray bond lengths are taken from the crystal structure of 7-ethyl-10-(4-piperidino)piperidinylcarbonyloxy CPT HCl [17].

All points in both the ab initio and MM3 torsional profiles were obtained by constraining the dihedral angles of interest. Unconstrained ab initio geometry optimizations of minima and transition states may result in a more complete energy profile, but in this study we have focused on energy barriers to rotation.

As shown in Table 2, dihedral angles in which the two central atoms are pi atom types (e.g. 37-2-2-151) have considerably larger V_2 contributions than do dihedrals in which the two central atoms are not pi atoms.

Conclusions

In conclusion, missing torsional parameters for the MM3 force field have been obtained for the α-hydroxy lactone and the natural product CPT using ab initio torsional profiles on representative compounds containing the critical dihedral angle. These parameters are scheduled for release in MM3(96). With these new parameters, conformational analysis for CPT and similar compounds may be undertaken. The similarity between the MM3 minimized α-hydroxy lactone, the two X-ray, and the ab initio structures supports the parameterization results for the two parameters involved in the lactone (2-1-75-3 and 75-1-2-3).

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