Molecular Mechanics (MM3) Conformational Studies of Cyclic and Acyclic Monochloroalkanes

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Molecular mechanics calculations play an important role in modern conformational analysis. Alkyl chlorides are useful organic compounds that have been used as important intermediates and target compounds of commercial and academic interest. Molecular modeling studies utilizing force field calculations have become very popular in the past decade, but in order to make quantitative predictions of unknown compounds it is critical to be able to calculate accurately the energy among conformational equilibrium structures and transition state barriers for known compounds of the same family. An MM3 force field for monochloroalkanes has been developed recently that accurately reproduces molecular structures and vibrational frequencies. This paper presents and compares MM3 calculations with experimental data (Raman, IR, ED, MW, and NMR) for selected cyclic and acyclic monochlorohydrocarbons.

Introduction

Alkyl halides are a very important class of organic compounds. They play important roles as key synthetic precursors for many types of compounds primarily through functional group conversion via nucleophilic substitution. Many natural products are alkyl chloride derivatives. The accurate calculations of molecular forces responsible for conformational preferences in cyclic and acyclic monochlorohydrocarbons are necessary in order to make reasonable conformational predictions. High-level *ab initio* calculations may be used for structural predictions, but they suffer from time constraints for large molecular systems. Force field calculations, however, have been demonstrated to be quite useful over the years for monofunctional hydrocarbons.

A recently developed MM3 monochlorohydrocarbon force field usually reproduces to within experimental error molecular structures.[1] The overall root mean square (rms) error for the averaged C−C and C−Cl bond lengths for a large set of compounds excluding *sec*-butyl chloride, neopentyl chloride, and 1-chloroadamantane was 0.004 Å, and the rms error for the vibrational frequencies was 37 cm^{-1}. The moments of inertia (r_g) are approximately 1% greater than the microwave values (r_α^0).

This paper presents some MM3-calculated thermodynamic quantities for conformationally flexible and restricted acyclic monochloroalkanes (ethyl chloride, *n*-propyl chloride, isopropyl chloride, *n*-butyl chloride, isobutyl chloride, *sec*-butyl chloride, *tert*-butyl chloride, 2-chloro-2-methylbutane, 1-chloro-2,2-dimethylpropane, 1-chloro-3,3-dimethylbutane, 2-chloro-2,3-dimethylbutane, 2-chloro-3,3-dimethylbutane, 2-chloro-2,3,3-trimethylbutane, 3-chloro-2,2,3-trimethylpentane, 3-chloro-2,2,3,4,4-pentamethylpentane, 3-chloro-2,2,3,5,5-pentamethylhexane, 2-bicyclo[2.2.2]octyl-2-chloropropane, and 2-adamantyl-2-chloro-3,3-dimethylbutane) and cyclic monochloroalkanes (cyclopentyl chloride, cyclohexyl chloride, 1-chloro-1-methylcyclohexane, *trans*-1-chloro-3-methylcyclohexane, 1-chloro-2,2-dimethylcyclohexane, 1-chloro-3,3-dimethylcyclohexane, 1-chloro-4,4-dimethylcyclohexane, 4-*tert*-butyl-1-chlorocyclohexane, and 4-*tert*-butyl-1-chloro-1-methylcylohexane). The molecular mechanics values are compared to those observed by various experimental methods (Raman, IR, ED, MW, and NMR) with overall good agreement.

Results and Discussion

One of the important achievements of molecular mechanics, which makes it so useful and applicable in organic chemistry, is the ability to accurately predict the energy differences between conformers. These numbers are often important or essential to understanding such things as NMR spectra. The conformational energy differences in general are well reproduced by the new force field, as shown below. Stable conformations of some monochloroalkanes are defined and represented in Figure 1.

(a) Conformational Energies. Conformational energy calculations on monochloroalkanes are summarized in Tables 1 and 2.

n-Propyl chloride is known to exist as two stable conformers, *trans* and *gauche*, with little energy difference between them. From various experiments at different temperatures,[2] the energy difference between the *trans* and *gauche* forms was determined to be in the range of roughly −0.5 to +0.5 kcal/mol. The energy difference (ΔE) between the *gauche* and the *trans* conformers of *n*-propyl chloride from MM2 is 0.24 kcal/mol, with the *trans* form being more stable.[3] MM3, using torsional constants that correctly reproduce the energy difference between equatorial and axial conformers of

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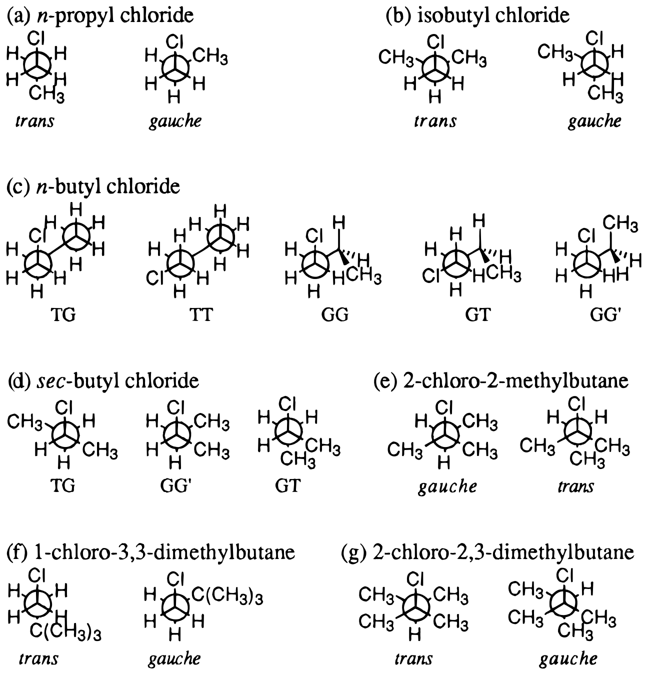

Figure 1. Conformations of monochloroalkanes.

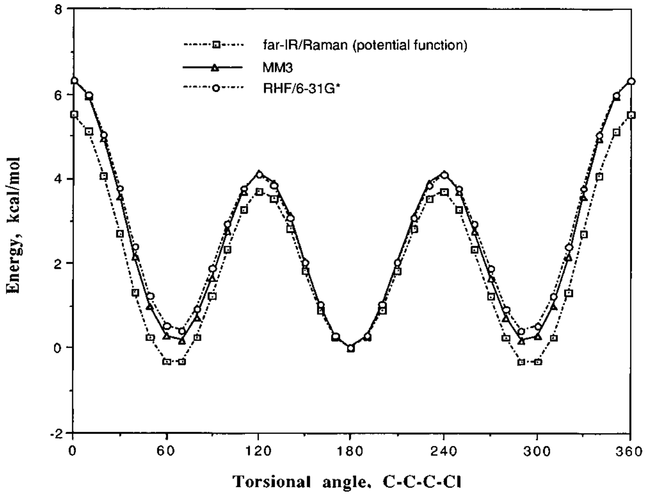

Figure 2. Torsional curves for *n*-propyl chloride generated from far-IR/Raman data as well as MM3 and RHF/6-31G* calculations. Far-IR/Raman spectra are derived from the observed spectra of lower asymmetric torsional transitions and are reported in ref 2g. MM3 and RHF/6-31G* are calculated by using dihedral driver for the fixed angle ∠(C−C−C−Cl) of 10° increment with optimizing all other geometric parameters.

cyclohexyl chloride, produces a 0.14 kcal/mol energy gap favoring the *trans* conformer. It is not easy to discern at present which experiment represents the correct energy difference between the *trans* and *gauche* isomers, since the measured values from various experimental methods were determined in different states and correspond to different thermodynamic quantities. The torsional curves for *n*-propyl chloride obtained by a far-IR/Raman study,[2g] as well as from MM3 and *ab initio* methods, are compared in Figure 2. The MM3 potential energy curve more closely resembles the one from RHF/6-31G* calculations than the one derived from the far-IR/Raman spectra, where the *gauche* form was determined to be of lower enthalpy than the *trans* form. The experimental conditions closest to our calculations are the Raman experiment by Ogawa et al.[2d] Their value of ΔH(*gauche*−*trans*) is 0.02 kcal/mol in the vapor phase and −0.09 kcal/mol in the liquid phase. Our corresponding value (ΔH) is 0.22 kcal/mol.

n-Butyl chloride exists as a mixture of several stable isomers, TG, TT, GG, GT, and GG′, depending upon the geometries of the terminal chlorine atom and the terminal methyl group. (The first symbol T or G refers to the terminal methyl and the second to the chlorine as shown in Figure 1.) MM3 calculates the TT form to be more stable than the TG form (in terms of ΔH) and the TT form to be less stable than the TG form (in terms of ΔG), whereas the TG form is the more stable (ΔH) on the basis of a liquid phase Raman experiment[2d] and both forms have the same energy (ΔG) from an electron diffraction experiment.[4] Again, this discrepancy is related to the *gauche* interaction between chlorine and γ-CH_2 group.

Isobutyl chloride exists as two stable conformers, *trans* and *gauche*. From the temperature-dependent gas phase Raman spectrum of isobutyl chloride, Durig et al.[5] calculated the enthalpy difference (ΔH) between the *gauche* and *trans* conformers to be 0.48 kcal/mol, with the *trans* conformer being higher in energy, which is more than the previously reported values: 0.22 kcal/mol by Wyn-Jones et al.[6] and 0.15 kcal/mol by Nomura et al.[7] *Ab initio* calculations[8] using the 4-31G basis set gave 0.38 kcal/mol of the energy difference (ΔE). MM3 correctly gives the *gauche* isomer to be 0.28 kcal/mol (ΔH) and 0.18 kcal/mol (ΔE) more stable than *trans* form.

It has been observed that *sec*-butyl chloride has three stable isomers, TG, GG′, and GT forms (see Figure 1). Our calculation shows that the GT isomer (with one 1,4-methyl−methyl repulsion) is more stable than the GG′ isomer (with one methyl−chlorine *gauche* interaction as well as one 1,4-methyl−methyl repulsion), which is opposite to the experimental results either from the liquid phase Raman[7] or the liquid phase IR.[9] The values determined spectroscopically are from the temperature-dependent ratios of C−Cl stretching frequencies[7] or CH_3 rocking frequencies[9] of each isomer. Possibly, the assignment for these frequencies, especially of less stable isomers (GT and GG′), is not correct, or bands overlap, since those isomers of this compound cannot be isolated. Therefore, their values for the energy differences seem doubtful.

Our calculations for longer chain monochloroalkanes with methyl substituents, such as 2-chloro-2-methylbutane and 2-chloro-2,3-dimethylbutane, also give values close to the experimentally determined ones[10,11] (see Table 1).

For cyclopentyl chloride, MM3 agreed with many experimental studies[12−15] that concluded that cyclopentyl

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Table 1. Conformational Thermodynamic Data^{a} for Selected Monochloroalkanes: MM3^{b} and Experiment

	$\Delta G°$	$\Delta H°$	$\Delta S°$	$\Delta E°$	T	method	ref^{j}
n-propyl chloride							
(*gauche*−*trans*)	0.12	−0.05	−0.56^{c}		298	ED+MW^{d}	1
		−0.47			296−343	Raman^{d}	2
	−0.12^{e}	−0.14			298−363	IR^{f}	3
		0.02,^{d} −0.09^{f}			168−288	Raman	4
	0				195, 298	MW^{d}	5
		0.05				IR^{d}	6
	−0.30, −0.60				298	ED^{d}	7
	−0.13	0.22	1.17	0.14	298	MM3	this work
n-butyl chloride							
(TT−TG)		0.15^{g}			168−288	Raman^{f}	4
(GG−TG)		0.21					
(GT−TG)		0.65					
(TT−TG)	0.0^{g}				291	ED^{d}	8
(GG−TG)	0.7						
(GT−TG)	1.2						
(GG′−TG)	1.2						
(TT−TG)	0.09	−0.25^{g}	−1.17	−0.18	298	MM3	this work
(GG−TG)	0.97	0.92	−0.14	0.79			
(GT−TG)	0.60	0.65	0.16	0.63			
(GG′−TG)	2.25	2.29	0.15	2.17			
isobutyl chloride							
(*trans*−*gauche*)	0.24	0.0			298	ultrasonic relaxation	9
		0.23				IR^{d,i}	10
		0.48			298−341	Raman^{d}	11
	0.12				301	ED^{d}	12
	0.76	0.28	−1.63	0.18	298	MM3	this work
sec-butyl chloride							
(GG′−TG)		0.55^{h}			233−313	Raman^{f}	10
(GT−TG)		0.60					
(GG′−TG)		0.58^{h}			163−303	IR^{f}	13
(GT−TG)		0.77					
(GG′−TG)	1.05	0.99^{h}	−0.19	0.85	298	MM3	this work
(GT−TG)	0.57	0.60	0.08	0.58			
2-chloro-2-methylbutane							
(*trans*−*gauche*)	0.29				138	NMR	14
		0.36	−1.38			ultrasonic relaxation	15
		1.1,^{d} 0.36^{f}				Raman^{i}	16
	0.62	0.45	−1.23	0.45	138	MM3	this work
1-chloro-3,3-dimethylbutane							
(*gauche*−*trans*)	1.08					NMR^{h}	17
		1.17				IR	18
	1.66	2.00	1.13	1.90	298	MM3	this work
2-chloro-2,3-dimethylbutane							
(*gauche*−*trans*)	0.10	0.29	1.37		138	NMR	19
	0.15	0.34	1.37	0.38	138	MM3	this work

[a] Free energy G in kcal/mol, enthalpy H in kcal/mol, entropy in cal/mol·K, and temperature T in Kelvin. [b] For the MM3 energy parameters, $\Delta E°$ was obtained from the final steric energy difference between the corresponding stable conformers, $\Delta H°$ and $\Delta S°$ were obtained from the thermodynamic part of MM3 output, and $\Delta G°$ was obtained from the $\Delta H°$ and the $\Delta S°$ at an appropriate temperature using the thermodynamic equation, $\Delta G° = \Delta H° - T\Delta S°$. [c] Only entropy of vibration and entropy of rotation were considered. For the entropy of these components, $\Delta S°$ of −0.20 cal/mol·K was obtained from MM3. [d] In the vapor phase. [e] From IR peak intensities. [f] In the liquid phase. [g] The enthalpy of the TG isomer from the corresponding method was taken as the reference. [h] The enthalpy of the S_{HH} isomer from the corresponding method was taken as the reference. [i] The temparuture range is not specified. [1]Reference 2f. [2]Reference 2g. [3]Tanabe. K.; Saeki, S. *J. Mol. Struct*. **1975**, *27*, 79. [4]Reference 2d. [5]Sarachman, T. N. *J. Chem. Phys.* **1963**, *39*, 469. [6]Reference 2a. [7]Reference 2b. [8]Reference 4. [9]Reference 27. [10]Reference 6. [11]Reference 5. [12]Schei, S. H.; Hilderbrandt, R. L. *J. Mol. Struct.* **1985**, *128*, 181. [13]Reference 9. [14]Reference 10a. [15]Reference 10b. [16]Reference 10c. [17]Whitesides, G. M.; Sevenair, J. P.; Goetz, R. W. *J. Am. Chem. Soc.* **1967**, *89*, 1135. [18]Oyama, T.; Takamizawa, K.; Shiokawa, M.; and Shiokawa, K. *Kyushu Diagaku Kogaku Shuho* **1979**, *52*, 113. [19]Reference 11.

chloride exists as two stable conformers, the axial and the equatorial envelope forms (C_s symmetry). MM3 calculated the axial isomer to be 0.75 kcal/mol (ΔH) more stable than equatorial isomer. This result is close to a value estimated from IR spectra in dilute CS_2 solution by Ekejiuba et al.[15] (see Table 2).

Since Atkinson's estimation from an electron diffraction study[16] in the early 1960s that the energy difference (ΔG) between the axial and equatorial conformers of cyclohexyl chloride is less than 0.26 kcal/mol, intensive experimental studies[17,18] have been carried out to examine the stable conformers of cyclohexyl chloride. The recently measured values are about 0.6 kcal/mol (ΔG)[17d,e] or in the range of 0.26−0.40 kcal/mol (ΔH) in solvents,

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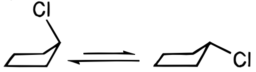
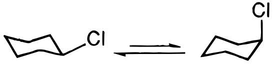
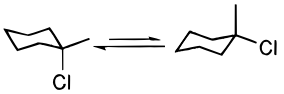
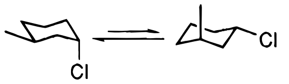
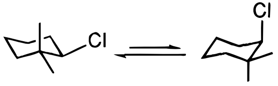
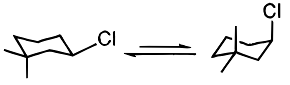
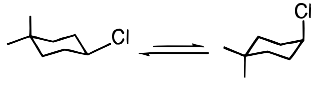
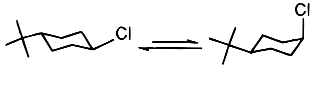
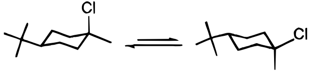
Table 2. Conformational Thermodynamic Data[a] for Selected Monochlorocycloalkanes: MM3[b] and Experiment

	ΔG^0	ΔH^0	ΔS^0	ΔE^0	T	Method	Ref.
Cyclopentyl chloride[c] 		0.34			153-298	Raman[e]	1
		0.70			123-363	IR[f]	2
	0.34				295	ED	3
	0.50	0.75	0.85	0.72	298	MM3	this work
Cyclohexyl chloride[d] 		0.26			233-383	Raman[e]	4
		0.40			133-298	IR[f]	5
	0.65				298	ED	6
	0.64	0.32	-1.1		175-195	NMR	7
				0.51	263	MW	8
	0.61	0.47	-0.46	0.33	298	MM3	this work
1-Chloro-1-methylcyclohexane[c] 	1.00	1.13	0.45		298	NMR	9
	1.1				298	IR[e]	10
	1.42	1.42	0.00	1.39	298	MM3	this work
trans-1-Chloro-3-methylcyclohexane[c] 	0.88[h]		0.87,[f] 0.82[g]		300-350	IR	11
	1.41	1.42	0.01	1.38	325	MM3	this work
1-Chloro-2,2-dimethylcyclohexane[d] 	0.99				170	NMR	12
	0.73	0.67	-0.37	0.60	170	MM3	this work
1-Chloro-3,3-dimethylcyclohexane[d] 	>1.5				193	NMR	13
	2.72	2.63	-0.48	2.44	193	MM3	this work
1-Chloro-4,4-dimethylcyclohexane[d] 	0.43				193	NMR	13
	0.54	0.47	-0.38	0.31	193	MM3	this work
4-*tert*-Butyl-1-chlorocyclohexane[d,i] 	0.49				298	NMR	14
	0.51	0.38	-0.47	0.22	298	MM3	this work
4-*tert*-Butyl-1-chloro-1-methylcyclohexar 	1.1				298	NMR	10
	1.48	1.47	-0.02	1.44	298	MM3	this work

[a] Free energy G in kcal/mol, enthalpy H in kcal/mol, entropy in cal/mol·K, and temperature T in Kelvin. [b] MM3 energy parameters for monochlorocycloalkanes were obtained in the same way for monochloroalkanes. [c] Cl-axial isomer is more stable than Cl-equatorial isomer. [d] Cl-equatorial isomer is more stable than Cl-axial isomer. [e] In the solid phase. [f] In the liquid phase. [g] In the vapor phase. [h] At 293 K. [i] In the presence of HCl. [1] Reference 14b. [2] Reference 15. [3] Reference 12. [4] Reference 17c. [5] Reference 17a. [6] Reference 17d. [7] Reference 17e. [8] Reference 17b. [9] Reference 19a (Carr). [10] Reference 19a (Allinger). [11] Reference 19b. [12] Reference 19c. [13] Reference 19d. [14] Reference 19f.

with the equatorial form being more stable than the axial (see Table 2). MM3 (gas phase) correctly calculates the equatorial form to be 0.61 kcal/mol ($\Delta G°$) and 0.47 kcal/mol ($\Delta H°$) more stable than the axial form.

In addition, methyl-, dimethyl-, and *tert*-butyl-substituted cyclohexyl chloride derivatives were examined to determine how their calculated ΔG or ΔH values agreed with the experimental data[17f,19] (see Table 2). The MM3 ΔG or ΔH energies are in very close agreement with experiment in all cases.

(b) Rotational Barriers. The different calculated and experimental rotational barriers for monochloroalkanes are listed in Table 3. The rotational barrier for ethyl chloride is calculated to be 3.63 kcal/mol from MM3, and it is close to the experimental values (3.58 kcal/mol from the torsional frequencies of the gas phase far-IR spectrum,[20] 3.56 kcal/mol or 3.68 kcal/mol from the microwave spectrum,[21,22] and 3.72 kcal/mol from the gas phase Raman spectrum of torsional fine structure[23]).

For *n*-propyl chloride, the MM3 rotational energy profile calculates the *trans* conformer as more stable (ΔH) than the *gauche*, and this is opposite to the results from an IR/Raman study[2g] where the *gauche* conformer was determined to be more stable. However, the total potential functions about the rotational barriers look very similar. On the other hand, the electron diffraction work[2b] shows that the *trans* conformation is somewhat more stable than the *gauche* (ΔG), as calculated by MM3.

For isopropyl chloride, the methyl rotational barrier was established to be 4.32 kcal/mol from gas phase far-IR[24] and 3.95 kcal/mol from Raman[25] experiments. This barrier has been calculated as 3.97 kcal/mol from MM3. Importantly, the results from the far-IR spectrum[24] and from MM3 calculations are supported by the conclusion from the microwave study[26] that the barrier is greater than 3.45 kcal/mol.

MM3 gave very similar rotational barriers for the *gauche* to *gauche* transition for isobutyl chloride ($\Delta H^{\ddagger} =$ 4.30 kcal/mol) and TG to GT conformation for *sec*-butyl chloride ($\Delta H^{\ddagger} = 4.53$ kcal/mol). This is reasonable because these operations involve the same type of steric interactions during rotations, i.e., two methyl−hydrogen interactions and one chlorine−hydrogen interaction. The experimentally determined rotational barrier for *sec*-butyl chloride was found by ultrasonic relaxation[6] and is almost identical with the MM3-calculated number. The experimentally determined rotational barrier for isobutyl chloride, by the same method,[27] is about 1 kcal/mol lower than what MM3 calculates.

For *tert*-butyl chloride, the methyl rotational barrier was roughly estimated to be 4 ± 2 kcal/mol from an electron diffraction study,[28] and Moller et al.[24] calculated the methyl rotational barrier to be 3.2 kcal/mol from the far-IR spectrum. This rotational barrier is too low when compared to the value of 4.51 kcal/mol calculated from the differently assigned torsional frequencies by Durig et al.[29] Durig's study yields a higher rotational barrier than either Moller's value[24] or the value from the temperature-dependent NMR (3.7 kcal/mol).[30] However, Durig's value[29] seems reasonable when compared to the rotational barriers of other related compounds, such as *tert*-butyl fluoride (4.3 kcal/mol, from microwave)[31] or *tert*-butyl bromide (3.9 kcal/mol, from IR).[29] From MM3, the rotational barrier of *tert*-butyl chloride has been calculated to be 4.31 kcal/mol.

Various monochlorohydrocarbons were examined with respect to their rotational barriers and compared to available experimental data. These include 2-chloro-2-methylbutane,[10b] 1-chloro-2,2-dimethylpropane,[10a] 2-chloro-2,3-dimethylbutane,[32] 2-chloro-3,3-dimethylbutane,[10a] 2-chloro-2,3,3-trimethylbutane,[33] 3-chloro-2,2,3-trimethylpentane,[34] 3-chloro-2,2,3,4,4-pentamethylpentane,[33] 3-chloro-2,2,3,5,5-pentamethylhexane,[33] 2-bicyclo[2.2.2]octyl-2-chloropropane,[35] and 2-adamantyl-2-chloro-3,3-dimethylbutane.[35] The results are summarized in Table 3. In general, the results are fairly good (at most less than 2 kcal/mol difference).

It was predicted from our dynamics calculations that the most likely transition state for cyclopentyl chloride (axial-to-equatorial envelope) has one imaginary vibrational frequency at -60.9 cm^{-1} (ring puckering) and is an equatorial half-chair form (C_2-like symmetry) with the energy being 1.79 kcal/mol higher than that of the axial envelope conformer (C_s symmetry). This value is close to the pseudorotational barrier to the axial-to-equatorial conversion, from other molecular mechanics calculations (1.1[36] or 1.17 kcal/mol[12]) and from the IR (<4 kcal/mol).[14]

From an analysis of the liquid IR spectrum of cyclohexyl chloride, Štokr et al.[17a] established barriers ($\Delta G^{\ddagger}$) of 10.9 and 10.5 kcal/mol for the interconversion of the equatorial to the axial form of cyclohexyl chloride. From an IR and NMR study of this molecule,[17e] values of 10.6 kcal/mol were determined for this barrier for both $\Delta G^{\ddagger}$ and $\Delta H^{\ddagger}$. Additionally, an energy difference ($\Delta H°$) of 0.32 kcal/mol was found between the axial and equatorial conformers favoring the equatorial. These results for cyclohexyl chloride are similar to those for cyclohexane which has a 10.8 kcal energy barrier ($\Delta H^{\ddagger}$) between the chair form and the twist form, and an energy difference

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Table 3. Thermodynamic Data of Rotational Barriers[a] for Selected Monochlorohydrocarbons: MM3[b] and Experiment

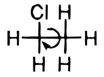
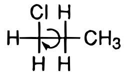
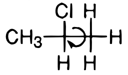
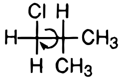
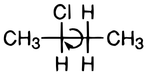
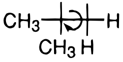
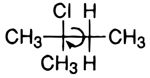
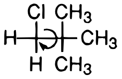
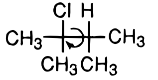
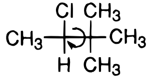
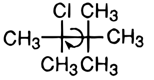
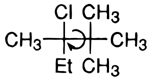
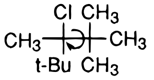
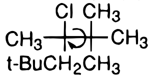
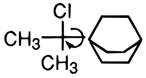
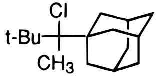
	ΔG‡	ΔH‡	ΔS‡	Temp.	Method	Ref.
Ethyl chloride						
						
		3.58		--	IR[c,d,e]	1
		3.68		--	MW	2
		3.72		--	Raman[c,d,e]	3
	4.11	3.63	-1.62	298	MM3	this work
n-Propyl chloride						
						
(*trans* -> *gauche*)		3.72		--	IR/Raman[c,d,e]	4
(*gauche* -> *trans*)		4.09				
(*gauche* -> *gauche'*)		5.89				
(*trans* -> *gauche*)	4.63	4.13	-1.66	298	MM3	this work
(*gauche* -> *trans*)	4.83	3.99	-2.84			
(*gauche* -> *gauche'*)	7.40	6.15	-4.23			
Isopropyl chloride						
						
		4.32		298	IR[c,d]	5
		3.95		298	Raman[c,d]	6
		3.45		195	MW	7
	4.06	3.97	-0.33	298	MM3	this work
Isobutyl chloride						
						
	5.76	5.26	-1.67	298	Ultrasonic relaxation	8
(*gauche* -> *gauche'*)	5.68	4.30	-4.61	298	MM3	this work
(*gauche'* -> *trans*)	7.97	6.88	-3.67			
(*trans* -> *gauche*)	7.30	6.70	-2.04			
sec-Butyl chloride						
						
		4.43		--	Ultrasonic relaxation[e]	9
(TG ->GT)	5.45	4.53	-3.08	298	MM3	this work
(GT ->GG')	6.76	5.62	-3.83			
(GG' ->TG)	7.17	6.18	-3.32			
tert-Butyl chloride						
						
	3.7			123-248	NMR	10
		4.51		83-163	IR[f]	11
	4.10	4.31	1.73	123	MM3	this work
2-Chloro-2-methylbutane						
						
		3.89		233-283	Ultrasonic relaxation	12
(*trans* -> *gauche*)	6.33	5.60	-2.45	298	MM3	this work
(*gauche'* -> *trans*)	7.14	6.05	-3.66			
(*gauche* -> *gauche'*)	8.26	6.81	-4.88			
1-Chloro-2,2-dimethylpropane						
						
	6.5			150	NMR	13
	7.55	7.21	-2.26	150	MM3	this work

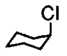
Table 3. (Continued)

	$\Delta G^\ddagger$	$\Delta H^\ddagger$	$\Delta S^\ddagger$	Temp.	Method	Ref.
2-Chloro-2,3-dimethylbutane 						
(*gauche* -> *gauche'*)	8.2			140	NMR	14
(*gauche'* -> *trans*)	7.4					
(*trans* -> *gauche*)	7.7					
(*gauche* -> *gauche'*)	8.18	7.57	-4.40	140	MM3	this work
(*gauche'* -> *trans*)	8.87	8.45	-3.03			
(*trans* -> *gauche*)	9.06	8.83	-1.67			
2-Chloro-3,3-dimethylbutane 						
	7.7	7.7	0	152	NMR	13
	9.38	8.89	-3.24	152	MM3	this work
2-Chloro-2,3,3-trimethylbutane 						
	10.43	8.9	-7.1	217	NMR	15
	11.95	10.84	-5.11	217	MM3	this work
3-Chloro-2,2,3-trimethylpentane 						
	10.82				NMR	16
	13.01	11.18	-6.15	298	MM3	this work
3-Chloro-2,2,3,4,4-pentamethylpentane 						
	11.42	11.84	2.1	213	NMR	15
	12.79	11.98	-3.80	213	MM3	this work
3-Chloro-2,2,3,5,5-pentamethylhexane 						
	11.76			212	NMR	15
	12.87	11.78	-5.16	212	MM3	
2-Bicyclo[2.2.2]octyl-2-chloro-propane 						
	9.8				NMR	17
	12.88	11.06	-6.10	298	MM3	this work
2-Admantyl-2-chloro-3,3-dimethylbutane 						
around *tert*-Butyl-C(Cl)	12.2				NMR	17
	13.62	12.64	-3.28	298	MM3	this work
around adamantyl-C(Cl)	10.6				NMR	17
	13.43	12.63	-2.71	298	MM3	this work
Cyclohexyl chloride						
(e->a)	10.6			173	IR[f]	18
(a->e)	10.2					
	10.6	10.6	0.0	228	NMR	19
(e->a)	10.24	10.75	2.25	228	MM3[g]	this work

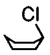
[a] Free energy G in kcal/mol, enthalpy H in kcal/mol, entropy in cal/mol·K, and temperature T in Kelvin. [b] In order to examine geometries for ground states and transition states, 5° increment torsional driver and full matrix minimization was used. For the MM3 energy parameters, $\Delta H^\ddagger$ was estimated to be equal to the final steric energy difference between the corresponding ground state and transition state, $\Delta S^\ddagger$ was obtained by subtracting $S°$ from $S^\ddagger$, and $\Delta G^\ddagger$ was obtained from the $\Delta H^\ddagger$ and the $\Delta S^\ddagger$ at an appropriate temperature using the thermodynamic equation, $\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$. [c] In the vapor phase. [d] Potential function is calculated. [e] The temperature is not specified. [f] In the solid phase. [g] For transition state, the half-chair equatorial form was used. [1]Reference 20a. [2]Reference 22. [3]Reference 23. [4]Reference 2g. [5]Reference 24. [6]Reference 25. [7]Reference 26. [8]Reference 27. [9]Reference 6. [10]Reference 30. [11]Reference 29. [12]Reference 10b. [13]Reference 10a. [14]Reference 32. [15]Reference 33. [16]Reference 34. [17]Reference 35. [18]Reference 17a. [19]Reference 17e.

Table 4. Possible Conformations and Transition States of Cyclohexyl Chloride with Their Energies (in kcal/mol) at 298 K by MM3

(a) stable conformations of cyclohexyl chloride

	chair (equatorial)	*chair* (axial)	*twist-boat* (equatorial)	*twist-boat'*	*twist-boat* (axial)
					
E	9.04	9.36	15.37	15.97	16.19
Erel	0.00	0.32	6.33	6.93	7.15

(b) transition states of cyclohexyl chloride

	boat (equatorial)	*half-twist* (equatorial)	*half-twist* (axial)	*boat* (axial)	*half-chair* (equatorial)	*half-chair* (axial)
						
E	15.63	17.10	17.17	17.25	19.78	19.99
Erel	6.59	8.06	8.13	8.21	10.74	10.95
imaginary vib. freq. (cm^{-1})	-69.5	-78.1	-74.4	-93.6	-223.3	-211.6
vibrational mode	Cβ-Cγ torsion	ring puckering	ring puckering	Cβ-Cγ torsion	ring puckering	ring puckering
symmetry	A"	A	A	A"	A'	A'

($\Delta H°$) of 5.5 kcal/mol between these two conformers.[37] It should be noted that $\Delta H^‡$ and $\Delta G^‡$ for cyclohexane are not the same because of a ΔS contribution to the ground state which arises from its symmetry number. Thus, $\Delta G^‡$ is lower in energy than $\Delta H^‡$ for cyclohexane, unlike cyclohexyl chloride.

From a conformational search using MM3, the interconversion of the stable equatorial to the axial chair conformation of cyclohexyl chloride was found to proceed through a stable twist-boat form. The stable conformations and the transition states with their energy values are presented in Table 4. Three twist-boat forms were found: two with chlorine equatorial and axial, the other with two equivalent positions (C_2-like symmetry) for chlorine. The energy differences (ΔE) between the equatorial chair and the equatorial and axial twist-boat conformations are 6.33 and 7.15 kcal/mol, respectively. The energy difference between the equatorial chair and the C_2-like twist-boat form was found to be 6.93 kcal/mol.

From these calculations, possible transition states (containing just one negative eigenvalue in the force constant matrix) are the equatorial and the axial boat forms, the equatorial and axial half-twist forms, and the equatorial and axial half-chair forms. The energy differences between the most stable equatorial chair isomer and these transition states are in the range of 6.59−10.95 kcal/mol. The transition state for the interconversion of twist-boat to twist-boat is very close in energy to the twist-boat conformations themselves. The half-twist forms were found to have lower energies than the corresponding half-chair forms where all carbons except the one bearing chlorine are in a same plane (see Table 4). Since the alternative half-chair form has a relatively high energy barrier due to the eclipsing interaction of the protons of the β-carbons, the interconversion process may occur without passing this state.

Conclusions

Molecular mechanics calculations have been proven to be effective tools over the years in conformational analysis for many different functional groups. Chlorinated compounds are of interest as chemical intermediates and target structures, and they are widely used in chemical processes and molecular design. A monochlorohydrocarbon force field has been recently developed (described elsewhere) on the basis of experimental and *ab initio* calculations and incorporated into the MM3(96) program. This paper has used the new force field to examine some interesting conformational properties associated with some monochlorohydrocarbons that have been studied with various experimental methods. MM3 is in good overall agreement with the available structural, conformational, and thermodynamic data, and the force field may be used with reasonable confidence in predicting the properties of new cyclic and acyclic alkyl chlorides.

Acknowledgment. We thank Tripos Associates and the Georgia Research Alliance for their support of this work.

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