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Molecular Mechanics (MM4) Studies of Carboxylic Acids, Esters, and Lactones

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MM4 force-field calculations have been extended to carboxylic acids, esters, and lactones. The related parameters were determined mainly by fitting to available experimental data and high-level ab initio calculations on simple molecules. The structures of the training-set molecules were well-reproduced with a rms errors of 0.005 Å for bond lengths and 0.8° for bond angles. The moments of inertia for 12 simple molecules of the title class were fit to the experimental (microwave) values with an overall rms error of 0.32%. The vibrational spectra were significantly improved from previous force-field calculations, with a rms error of 19 cm^{-1} for 74 frequencies of 5 compounds. The conformational equilibria and rotational barriers were also fit, approximately within experimental error. Although the calculated heats of formation for the carboxyl acids and esters were also improved relative to values in earlier work (MM3), the standard deviation of the heats for 30 selected compounds is still high (0.67 kcal/mol) compared to those for other classes of compounds previously studied with MM4.

Introduction

The aliphatic carboxylic acids have been known since the early days of organic chemistry. Most of the common ones were named after their sources because their chemical structures were not known at the time of their discovery, and these common names are still widely used today. For example, formic acid refers to ants, acetic acid refers to wine, and caproic acid refers to goat fat. The long-chain carboxylic acids (fatty acids) are very important in the biological sciences because they are the building blocks for lipids, which are in turn both important sources of energy and of structural material for the cell. Therefore, our goal here is to develop a better force field for simple carboxylic acids and their ester derivatives so that the improved force field can be used for more accurate future studies of lipids.

Since the new generation force field MM4 for saturated hydrocarbons was published in 1996,[1] several classes of functionalized molecules have been subsequently studied and added into the MM4 force field. These groups include alkenes,[2] conjugated hydrocarbons,[3] sulfides,[4] aldehydes/ketones,[5] alcohols/ethers,[6] amines,[7] and amides.[8] In this paper, we report our MM4 study of the carboxylic acids and their ester and lactone derivatives.

The previous MM3 force field did a reasonable job of giving structures and energies for carboxylic acids and esters.[9] However, because of the lack of some important cross terms, such as torsion−bend and bend−torsion−bend, MM3 fell short of giving good predictions of moments of inertia as well as vibrational spectra for some key compounds. MM3 gave an overall rms error of 1.27% (0.77%, if (*E*)-formic acid and ethyl formates were excluded) for the moments of inertia of the selected 12 acids and esters. The error is large compared to those for other functionalized compounds calculated by MM3. Although MM3 gave reasonably good vibrational frequency calculations for this type of compound (overall rms error 30 cm^{-1}), some frequencies were off by as much as 90 cm^{-1}. The MM3 heat-of-formation calculations are also not as good as those for other functionalized molecules, and the standard deviation for the 30 selected compounds was 1.14 kcal/mol. Although the discrepancy appears to be mainly due to the large experimental uncertainties, the MM3 error was still far greater than the stated experimental error (av ±0.44 kcal/mol). Because more cross terms have been included in the current MM4 force field, we expect that improvements in the structure and frequency calculations for carboxylic acids and esters can be achieved. In the next few sections, the MM4 force-field parametrization procedure will be described first, and then the discussion of the structures and conformational energies for key acids, esters, and carboxylic acid dimers will be presented. At the end, we will focus on the vibrational spectra and heat-of-formation calculations. After the simple molecules in the gas phase are reasonable in hand, the tests of newly developed parameters (Table 1S, Supporting Information) on condensed-phase (X-ray crystal) structures are briefly discussed in the final section of this report.

Force Field. The MM4 force field begins with the same set of superimposed potential functions used in MM3.[10] Various additional cross terms were then introduced into the MM4 force field. Among them, the torsion−bend, bend−torsion−bend, stretch−stretch, and type 2 torsion−stretch (terminal bond) interactions are considered to be the key cross terms for the improvement of MM4 calculations for several functional groups, including the carboxyl group reported in this study. These additional cross terms used in MM4 are as follows.

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Torsion−Bend:

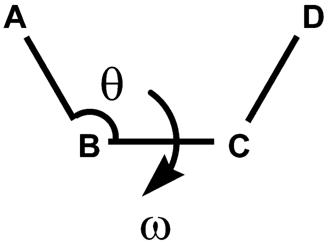


Figure 1. Illustration of torsion−bend interaction.

$$E_{\mathrm{tb}} = 2.51124[K_{\mathrm{tb1}}(1 + \cos\omega) + K_{\mathrm{tb2}}(1 - \cos 2\omega) + K_{\mathrm{tb3}}(1 + \cos 3\omega)](\theta - \theta°)$$

Bend−Torsion−Bend:

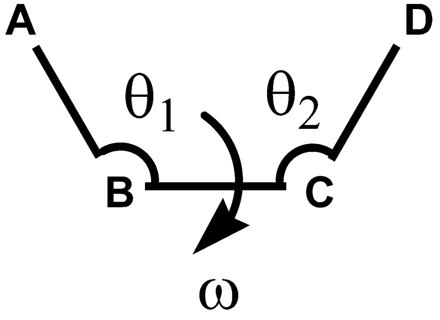


Figure 2. Illustration of bend−torsion−bend interaction.

$$E_{\mathrm{btb}} = 0.043828K_{\mathrm{btb}}(\theta_1 - \theta_1°)\cos\omega\,(\theta_2 - \theta_2°)$$

Stretch−Stretch:

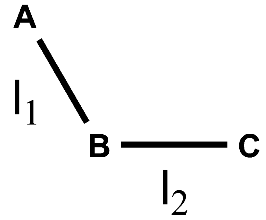


Figure 3. Illustration of stretch−stretch interaction.

$$E_{\mathrm{ss}} = 143.88K_{\mathrm{ss}}(l_1 - l_1°)(l_2 - l_2°)$$

Torsion−Stretch (Terminal Bond):

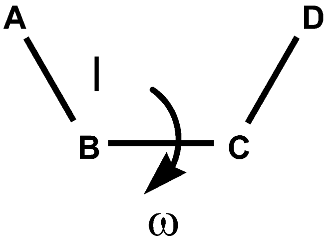


Figure 4. Illustration of torsion−stretch (terminal bond) interaction.

$$E_{\mathrm{ts}} = -0.5[K_{\mathrm{ts1}}(1 + \cos\omega) + K_{\mathrm{ts2}}(1 - \cos 2\omega) + K_{\mathrm{ts3}}(1 + \cos 3\omega)](l - l°)$$

Parametrization. Our MM4 parametrization strategy for acids, esters, and lactones is the same as the one used in the development of the previous force field, MM3. The basic approach is to develop a force field that fits the available structural, spectroscopic, and energetic data for simple molecules in the isolated environment (gas phase). The force field is then tested on other more complicated systems, including condensed phases. The gas-phase force field may extend to condensed phases by the use of standard approximations.

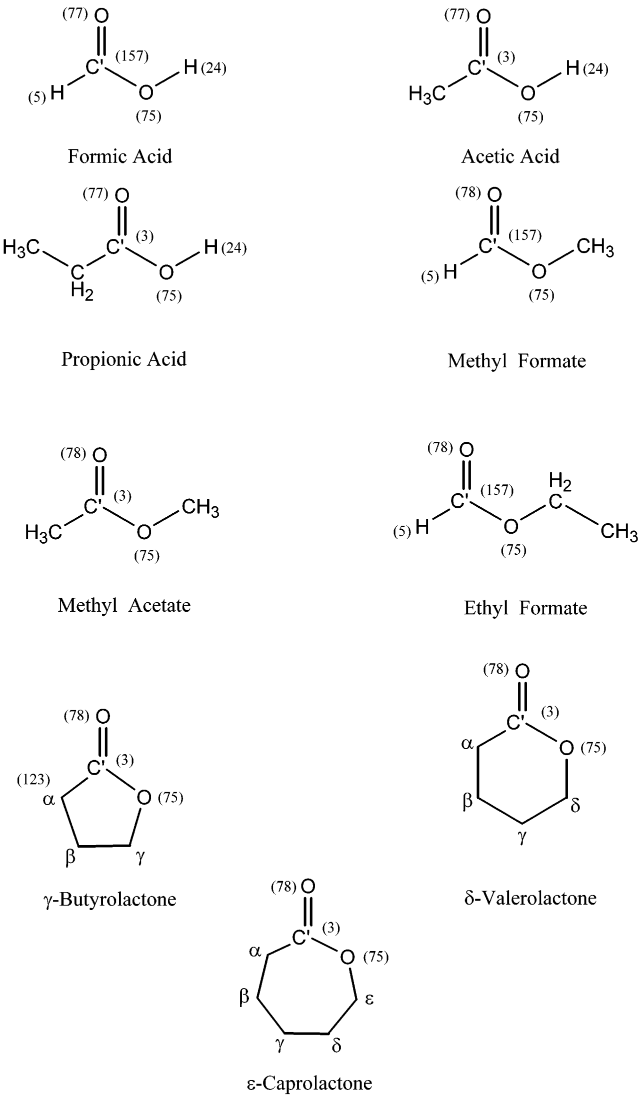


Figure 5. Structures and atom types (shown in parentheses) of acids, esters, and lactones used in the MM4 parametrization.

Structures. The training set used in the structural parametrization for the title-class compounds includes formic acid, acetic acid, propionic acid, methyl formate, methyl acetate, γ-butyrolactone (five-membered ring), δ-valerolactone conformations (boat and half-chair, six-membered ring), and ϵ-caprolactone (chair, seven-membered ring). The MM4 atom types used for these compounds are mostly the same as those used for MM3, except that the atom type of the carbonyl carbon was changed from type 3 to type 157 for formic acid and formates to be consistent with the atom types assigned to the aldehydes.[5] The structures and atom types (shown in parentheses) for these training compounds are shown in Figure 5. Fortunately, there are many good electron diffraction and microwave structural data available for these small molecules. Our approach was to try to fit the geometries of the training compounds to experimental values (especially moments of inertia) and to simultaneously try to fit those to the high-level ab initio MP2/6-311++G(2d,2p) results using the Gaussian[11] program. This approach could not be smoothly utilized with the MM3 parametrization because the 3-D structure conversions among the thermally averaged structures (r_g or r_a), microwave structures (r_z and r_s), and equilibrium structures (r_e) were not well established with MM3.[12] To interconvert 3-D structures, MM3 uses a least-squares fitting procedure to optimize the corrected bond lengths while keeping all bond angles and torsion angles as close to those of the r_g structure as possible. However, with MM4, the conversions of 3-D structures among r_g, r_e, r_z, and r_s structures are carried out by optimizing all of the corrected atomic distances (including bonded and nonbonded distances) using a full-matrix optimizer and by allowing all bond angles and torsion angles to relax to their optimum values.[13] This improved procedure makes the bond angles and torsion angles closer to their expected values when the vibrational corrections are applied. The calculated structures were systematically analyzed and are compared to the experimental and ab intio values. The parameters were then properly adjusted to get a better fit with a least-squares method.

Conformational Energies. The training set for the rotational barrier and conformational equilibria parametrization contains formic, acetic, and propionic acids, methyl, ethyl, and *n*-propyl formate, methyl acetate, methyl propionate, and methyl α-methylpropionate. A total of fifteen torsional potential profiles were investigated. These profiles were constructed by rotating one at a time the O═C′−O−H, O═C′−O−C, O═C′−C$_\alpha$−H, O═C′−C$_\alpha$−C$_\beta$, C′−O−C−H, and C′−O−C−C dihedral angles using 30° intervals. Quantum mechanical (QM) calculations using the Becke3LYP/6-311++G(2d,2p) DFT theory were carried out for all 15 torsional potential profiles. The Becke3LYP DFT (instead of MP2) theory was chosen here because of the computing time involved as well as concerns about the intramolecular basis set superposition errors (BSSE). According to our previous carbohydrate study,[14] Becke3LYP theory usually gives a smaller BSSE than MP2 when hydrogen bonding is involved. These rotational energy profiles were then combined for the MM4 torsional parameter optimization. A total of 15 types of torsional parameters, which are necessary in the study (see Table 1S), were optimized simultaneously using the least-squares fitting program TORSFIND.[15] The procedure allowed us to update all related torsional parameters at the same time whenever other parameters, such as stretching or bending, were significantly changed. Some of these optimized torsional parameters were then fine tuned to fit to the experimental conformational energies and rotational barriers.

Vibrational Frequencies. Seventy-four experimental vibrational frequencies for five simple molecules were investigated. These compounds are formic acid, acetic acid, methyl formate, methyl acetate, and γ-butyrolactone. Frequencies with uncertain assignments were checked against the QM (Becke3LYP/6-31G**)[16] frequencies, which were scaled using the force-constant scaling procedure FSCALE[17] that is based on the algorithm suggested by Pulay.[18]

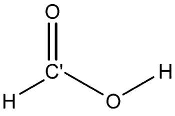
Results and Discussion

Geometries and Conformational Energies. Like its predecessor, MM4 can be used to calculate the r_g structure by default. The structures are comparable to gas-phase electron diffraction (GED) values. However, MM4 also has the ability to convert r_g structures to r_z/r_s (microwave) and r_e (equilibrium) structures. Therefore, we can fit the MM4 r_g bond lengths and angles to the GED experimental values and at the same time fit the MM4 r_z moments of inertia to the experimental microwave values. Because the moments of inertia are the most accurate direct information that one can get from experiment, we usually focus on fitting moments of inertia accurately when we cannot fit both values at the same time. We also fit the MM4 r_e bond lengths and angles to the ab initio MP2/6-311++G(2d,2p) values whenever experimental bond lengths and angles are in doubt. Perhaps somewhat unexpectedly, we usually can fit the r_z, r_e, and r_g structures at the same time very well. This gave us more confidence in the accuracy of the r_e structures calculated by MP2/6-311++G(2d,2p) theory as well as the conformational energies calculated by Becke3LYP/6-311++G(2d,2p) theory.

Formic Acid. Two stable formic acid rotomers, Z and E, are reported experimentally. The Z conformer, in which the carboxylic hydrogen is eclipsed to the carbonyl C′═O bond, is reported to be more stable. For (*Z*)-formic acid, Almenningen et al.[19] reported a GED r_g structure in 1969. Kwie and Curl[20] published a microwave r_s structure in 1960, and Bellet et al.[21] reported microwave moments of inertia as well as an r_s structure in 1971. However, Bellet's r_s structure is far too different from the other experiment results. For (*E*)-formic acid, a microwave r_s structure was reported by Bjarnov and Hocking[22] in 1978, and the moments of inertia were reported by Hocking[23] in 1976. These experimental data, along with the MM3 and MM4 results, are summarized in Table 1. Compared to those of MM3, the MM4 results are significantly improved, mainly because of the introduction of torsion−bend cross terms and the new carbonyl carbon atom type (157). As was discussed for aldehydes and ketones, a carbonyl carbon attached to a hydrogen is approximately, but not exactly, equivalent to one attached to an alkyl group. If the same atom type is used for both, the accuracy of the results is limited unnecessarily. All MM4 bond lengths and moments of inertia for both (*Z*)-formic acid and (*E*)-formic acid are in fair agreement with the reported values, except the C′═O r_g bond length for (*Z*)-formic acid. The r_g bond length for this bond is reported as 1.217(3) Å,[19] whereas the MM4 value is shorter by 0.012 Å. However, because the MM4 r_s and r_e values for this bond, as well as the moments of inertia, are in good agreement with those reported and QM values for both conformers, we conclude that the experimental value is just not very accurate. Besides, both MM4 and high-level QM calculations and even microwave r_s values show that C′═O bond lengths increase as chain length increases from formic acid to propionic acid, whereas the experimental r_g values show otherwise. Both experimental and QM results show that the C′═O bond is longer in the Z form than in the E form (r_s: 1.202 vs 1.195 Å, respectively), but the trend in the C′−O bond length is the reverse (r_s: 1.343 vs 1.352 Å, respectively). These phenomena can be explained by the fact that the lone pairs on the carboxylic oxygen are better positioned for O═C′−O resonance ($n \rightarrow \pi^*$) in the Z conformer (see Figure 6).

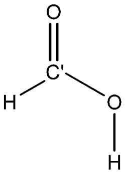
The resonance not only causes the C′−O to shorten and the O═C′ to lengthen but also stabilizes the Z form and increases the Z → E rotational barrier to some extent.[24] The Z conformer is reported to be 3.90 ± 0.09 kcal/mol more stable than the E conformer from microwave intensity measurements by Hocking.[23] The Z ⇄ E equilibrium energy and the Z → *E* and E → Z barriers were calculated to be 4.16, 12.87, and 8.71 kcal/mol, respectively, with the Becke3LYP/6-311++G(2d,2p) theory, whereas MM4 gave a value of 3.90 kcal/mol in favor of the Z form and values of 12.80 and 8.89 kcal/mol for the two rotational barriers (see Table 2). The moments of inertia for both conformers are improved significantly in the MM4 calculations versus MM3 (see Table 1). This improvement mainly comes from the better fit of the O═C′−O angles with MM4. The r_s values of these angles are reported as 124.9° and 122.1° for Z and E conformers, respectively, from the microwave studies.[20,22] However, MM3 gave almost the same values

TABLE 1: Structural Data from Experiment, MM3, and MM4 for Formic Acid[a]



(Z)-formic acid

	exp (r_g)[b]	MP2/6-311++G(2d,2p)	exp (r_s)[c]	MM3 (r_g)[d]	MM4 (r_g)	MM4 (r_e)	MM4 (r_s)
C′=O	1.217 (3)	1.2052	1.202 (10)	1.2112 (−0.0058)	1.2054 (−0.0116)	1.2005 (−0.0047)	1.2023 (+0.0003)
C′−O	1.361 (3)	1.3498	1.343 (10)	1.3358 (−0.0252)	1.3525 (−0.0085)	1.3466 (−0.0032)	1.3489 (+0.0059)
C′−H	1.106 (3)	1.0905	1.097 (5)	1.1051 (−0.0009)	1.1028 (−0.0032)	1.0845 (−0.0060)	1.0885 (−0.0085)
O−H	0.984 (3)	0.9674	0.972 (5)	0.9738 (−0.0102)	0.9821 (−0.0019)	0.9671 (−0.0003)	0.9671 (−0.0049)
O=C′−O	123.4 (5)	125.0	124.9 (10)	123.8 (0.4)	124.6 (+1.2)	123.8 (−1.2)	124.0 (−0.9)
O−C′−H	109.1 (88)	109.8	111.0 (20)	112.1 (+3.0)	110.2 (+1.1)	110.6 (+0.8)	110.5 (−0.5)
C′−O−H	107.3 (44)	106.7	106.3 (10)	107.3 (+0.0)	105.7 (−1.6)	106.8 (+0.1)	106.6 (+0.3)
			exp (r_z)[e]	MM3 (r_g)[d]			MM4 (r_z)
I_a			1.0965	1.1089 (+1.13%)			1.0992 (+0.25%)
I_b			6.9610	6.9014 (−0.86%)			6.9774 (+0.24%)
I_c			8.0575	8.0103 (−0.59%)			8.0691 (+0.14%)
μ		1.735	1.420[f]	1.730 (+0.310)[d]			1.443 (+0.023)



(E)-Formic Acid[a]

	exp (r_g)	MP2/6-311++G(2d,2p)	exp (r_s)[g]	MM3 (r_g)[h]	MM4 (r_g)	MM4 (r_e)	MM4 (r_s)
C′=O		1.1985	1.195 (3)	1.2127	1.1985	1.1938 (−0.0047)	1.1955 (−0.0030)
C′−O		1.3570	1.352 (3)	1.3394	1.3524	1.3465 (−0.0105)	1.3490 (−0.0030)
C′−H		1.0970	1.105 (4)	1.1074	1.1102	1.0914 (−0.0056)	1.0955 (−0.0095)
O−H		0.9624	0.956 (5)	0.9738	0.9761	0.9614 (−0.0010)	0.9614 (+0.0054)
O=C′−O		122.4	122.1 (4)	124.0	122.4	121.9 (−0.5)	122.0 (−0.1)
O−C′−H		113.5	114.6 (6)	113.8	112.3	112.4 (−1.1)	112.3 (−2.3)
C′−O−H		108.8	109.7 (4)	109.5	108.6	109.5 (+0.7)	109.4 (−0.3)
			exp (r_z)[i]	MM3 (r_g)[h]			MM4 (r_z)
I_a			0.9706	0.9409 (−3.06%)			0.9724 (+0.19%)
I_b			7.1794	7.3173 (+1.92%)			7.1908 (+0.16%)
I_c			8.1604	8.2582 (+1.20%)			8.1561 (−0.05%)
μ		4.405	3.790[i]	3.890 (+0.100)[h]			3.769 (−0.021)

[a] Bond lengths in Å; bond angles in degrees; moments of inertia in 10^{-39} g cm^2, and dipole moment in debye. [b] Reference 19. [c] Reference 20. [d] Reference 9. [e] Reference 21. [f] Reference 47. [g] Reference 22. [h] Reference 9. [i] Reference 23.

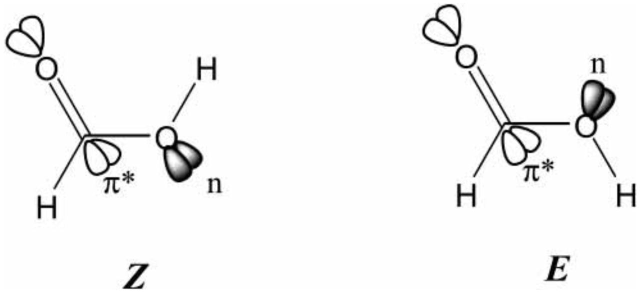


Figure 6. Rotational isomers of formic acid.

(r_g: 123.8° and 124.0°, respectively) for both conformers. This discrepancy was corrected in the MM4 calculations by the introduction of a torsion−bend interaction to reflect the O=C′−O angle changes due to the stronger resonance effect in the Z conformer. MM4 now gives r_s values of 124.0° and 122.0° for Z and E conformers, respectively.

Acetic Acid. In 1971, Derissen[25] reported an r_g structure for acetic acid. In 1981, Van Eijck et al.[26] published an r_s structure for this compound. Table 3 summarizes the MM3 and MM4 results and the experimental data. Like that from MM3, the MM4 r_g structure is very different from Derissen's GED structure. The r_g value of the C′−C$_\alpha$ bond length seems to be too long in Deriseen's report because both the microwave study and the MP2/6-311++G(2d,2p) calculation show otherwise. Also, the bond is expected to be significantly shorter than that in acetone[5] because of the electronegative effect of the attached C′−O bond. But Derissen's bond length is instead longer (1.520 vs 1.518 Å). Furthermore, Derissen's structure gives moments of inertia that are too large relative to the microwave values, as pointed out in the MM3 study.[9] All of these facts show that Derissen's C′−C$_\alpha$ bond length is in question. The experimental r_g and r_s and QM r_e values for this bond are 1.520, 1.494, and 1.500 Å, respectively. The MM4 calculated values were 1.503, 1.498, and 1.495 Å, respectively. There is no experimental structure reported for the (E)-acetic acid conformer because its conformational energy is so much higher than that of the Z conformer because of the steric effect from the methyl group. Table 2 shows the QM results for the Z $\rightleftarrows$ E equilibrium energy and the Z → E and E → Z barriers. These have values of 5.33, 12.77, and 7.43 kcal/mol, respectively. The MM4 calculated results for these energies are 5.35, 12.76, and 7.41 kcal/mol, respectively. The methyl group rotational barrier that was studied

TABLE 2: Conformational Energies and Rotational Barriers for Selected Acids and Esters[a]

	exp [ref]	Becke3LYP/ 6-311++G(2d,2p)	MM3	MM4
	Formic Acid			
$\Delta E_{\mathrm{E-Z}}$	3.900(85) [23]	4.160	3.950	3.904
$\Delta E_{\mathrm{Z\rightarrow E\ barrier}}$		12.870	12.850	12.796
$\Delta E_{\mathrm{E\rightarrow Z\ barrier}}$		8.710	8.900	8.891
	Acetic Acid			
$\Delta E_{\mathrm{E-Z}}$		5.333	4.976	5.347
$\Delta E_{\mathrm{Z\rightarrow E\ barrier}}$		12.766	13.240	12.759
$\Delta E_{\mathrm{E\rightarrow Z\ barrier}}$		7.432	8.265	7.412
$\Delta E_{\mathrm{methyl\ barrier}}$	0.483(25) [27] 0.4808(5) [28]	0.363	0.402	0.472
	Propionic Acid			
$\Delta E_{\mathrm{E-Z}}$		5.114	4.994	5.305
$\Delta E_{\mathrm{Z\rightarrow E\ barrier}}$		12.369	13.249	12.727
$\Delta E_{\mathrm{E\rightarrow Z\ barrier}}$		7.255	8.255	7.422
$\Delta E_{\mathrm{methyl\ barrier}}$	2.34(3) [31]	2.151	2.881	2.186
$\Delta E_{\mathrm{ethyl\ barrier}}$		1.394	1.833	1.616
	Methyl Formate			
$\Delta E_{\mathrm{E-Z}}$	4.75(19) [35] 3.85(20) [34]	4.940	4.844	4.773
$\Delta E_{\mathrm{Z\rightarrow E\ barrier}}$		13.523	16.511	13.664
$\Delta E_{\mathrm{E\rightarrow Z\ barrier}}$		8.582	11.667	8.892
$\Delta E_{\mathrm{methoxyl\ barrier}}$	1.19(4) [33]	0.778	1.136	1.170
	Methyl Acetate			
$\Delta E_{\mathrm{E-Z}}$	8.5(10) [35]	7.541	8.713	7.526
$\Delta E_{\mathrm{Z\rightarrow E\ barrier}}$		13.115	17.373	13.319
$\Delta E_{\mathrm{E\rightarrow Z\ barrier}}$		5.574	8.660	5.793
$\Delta E_{\mathrm{methyl\ barrier}}$	0.285(1) [37]	0.210	0.403	0.278
$\Delta E_{\mathrm{methoxyl\ barrier}}$	1.217(8) [37]	0.838	1.203	1.186
	Ethyl Formate			
$\Delta E_{\mathrm{gauche-trans}}$	0.186(60) [42]	0.414	0.186	0.217
$\Delta E_{\mathrm{trans\rightarrow gauche\ barrier}}$	1.100(250) [42]	0.747	1.249	0.850
$\Delta E_{\mathrm{gauche\rightarrow gauche\ barrier}}$	5.2(25) [42]	6.453	3.454	7.655

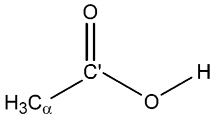
[a] All energies are in kcal/mol.

with the microwave method was reported to be 0.483(25) kcal/mole by Tabor[27] in 1957 and 0.4808(5) kcal/mole by Krisher and Saegebarth[28] in 1971. Our QM and MM4 values for this barrier are 0.363 and 0.472 kcal/mol, respectively (see Table 2).

Propionic Acid. The structure of propionic acid is very similar to that of acetic acid, according to experiment. In 1971, Derissen[29] reported a high-temperature GED investigation of the structure of propionic acid. A microwave r_s structure and moments of inertia for this compound were reported by Stiefvater[30,31] in 1975. Table 4 shows that the MM4 r_s and r_e structures as well as the moments of inertia for propionic acid are in good agreement with the experiment and with high-level QM results. However, the MM4 r_g structure is less comparable to Derissen's structure. The MM4 calculated r_g bond lengths of the $C'-C_\alpha$ and $C_\alpha-C_\beta$ bonds are shorter by 0.010 and 0.012 Å, respectively. Derissen's r_g bond lengths are systematically too long for both acetic acid and propionic acid because they are inconsistent with the experimental moments of inertia. This discrepancy might be due in part to the fact that the experiments were done at high temperatures in the gas phase for the monomer (160 °C for acetic acid and 215 °C for propionic acid). The larger vibrational amplitudes in the high-temperature experiments would cause weaker bonds such as the $C'-C_\alpha$ and $C_\alpha-C_\beta$ bonds to stretch more from anharmonicity. The $Z \rightleftarrows E$ equilibrium energy and the $Z \rightarrow E$ and $E \rightarrow Z$ rotational barriers for propionic acid are very similar to those for acetic acid. They are 5.11, 12.37, and 7.26 kcal/mol, respectively, from QM calculations and 5.31, 12.73, and 7.42 kcal/mol, respectively, from MM4 calculations (see Table 2). The rotational barrier of the terminal methyl group that was studied by the microwave method was reported to be 2.34(3) kcal/mole by Stiefvater[31] in 1975. The QM and MM4 calculations for this barrier are 2.15 and 2.19 kcal/mol, respectively. There is no reported experimental ethyl group rotational barrier for propionic acid. The QM and MM4 ethyl group rotational barriers for propionic acid were calculated to be 1.39 and 1.62 kcal/mol, respectively.

Methyl Formate. In 1980, Cradock and Rankin[32] reported a GED r_a structure for methyl formate. It was later converted to an r_g structure in the MM3 study of acids and esters.[9] A microwave r_s structure and moments of inertia were reported by Curl[33] in 1959. These experimental data along with the ab initio MP2/6-311++G(2d,2p) and MM4 results for this compound are summarized in Table 5. This Table shows that all r_g, r_e, and r_s $C'-O$ bond lengths for this compound are systematically shorter than those for formic acid by ~0.007−0.018 Å. These bond-shortening phenomena cannot be explained by the electronegativity effect caused by the attached methyl group in methyl formate because the methyl group is regarded as an electron-donating rather than an electron-withdrawing group.

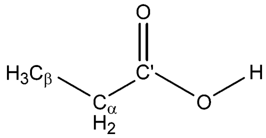
TABLE 3: Structural Data from Experiment, MM3, and MM4 for Acetic Acid[a]



	exp (r_g)[b]	MP2/6-311++G(2d,2p)	exp (r_s)[c]	MM3 (r_g)[d]	MM4 (r_g)	MM4 (r_e)	MM4 (r_s)
$C'{=}O$	1.214 (3)	1.2101	1.209 (6)	1.2126 (−0.0014)	1.2134 (−0.0006)	1.2089 (−0.0012)	1.2100 (+0.0010)
$C'-O$	1.364 (3)	1.3607	1.357 (5)	1.3657 (+0.0017)	1.3582 (−0.0058)	1.3517 (−0.0090)	1.3537 (−0.0031)
$C'-C_\alpha$	1.520 (5)	1.5000	1.494 (10)	1.4906 (−0.0294)	1.5027 (−0.0173)	1.4953 (−0.0047)	1.4982 (+0.0042)
$O-H$	0.970[f]	0.9666	0.970 (3)	0.9739	0.9817	0.9668 (+0.0002)	0.9668 (−0.0032)
$O{=}C'-O$	122.8 (6)	122.5		121.8 (−1.0)	122.5 (−0.3)	122.3 (−0.2)	122.3
C_α-$C'{=}O$	126.6 (6)	126.2	126.2 (7)	126.2 (−0.4)	125.7 (−0.9)	125.8 (−0.4)	125.8 (−0.4)
$O-C'-C_\alpha$	110.6 (6)	111.3	112.0 (6)	112.0 (+1.4)	111.8 (+1.2)	112.0 (+0.7)	111.9 (−0.1)
$C'-O-H$	107.0	106.0	105.9 (5)	107.4 (+0.4)	105.2 (−1.8)	106.2 (+0.2)	106.1 (+0.2)
			exp (r_z)[e]	MM3 (r_g)[d]			MM4 (r_z)
I_a			7.4034	7.4542 (+0.69%)			7.4069 (+0.05%)
I_b			8.8537	8.9172 (+0.72%)			8.8766 (+0.26%)
I_c			15.7598	15.8333 (+0.47%)			15.7861 (+0.17%)
μ		2.006	1.700[e]	1.690 (−0.010)[d]			1.673 (−0.027)

[a] Bond lengths in Å; bond angles in degrees; moments of inertia in 10^{-39} g cm^2, and dipole moment in debye. [b] Reference 25. [c] Reference 26. [d] Reference 9. [e] Reference 28. [f] Asummed value.

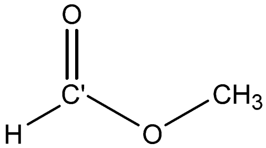
TABLE 4: Structural Data from Experiment, MM3, and MM4 for Propionic Acid[a]



	exp (r_g)[b]	MP2/6-311++G(2d,2p)	exp (r_s)[c]	MM3 (r_g)[d]	MM4 (r_g)	MM4 (r_e)	MM4 (r_s)
C′═O	1.211 (3)	1.2105	1.210 (1)	1.2127 (+0.0017)	1.2161 (+0.0051)	1.2117 (+0.0012)	1.2126 (+0.0026)
C′−O	1.367 (4)	1.3614	1.352 (2)	1.3659 (−0.0011)	1.3605 (−0.0065)	1.3540 (−0.0074)	1.3547 (+0.0027)
C′−C_α	1.518 (10)	1.5047	1.509 (2)	1.4955 (−0.0225)	1.5080 (−0.0100)	1.5005 (−0.0042)	1.5032 (−0.0058)
O−H		0.9667	0.970 (1)	0.9739	0.9817	0.9668 (+0.0001)	0.9668 (−0.0032)
C_α−C_β	1.543(10)	1.5206	1.523 (3)	1.5279 (−0.0151)	1.5307 (−0.0123)	1.5240 (+0.0034)	1.5242 (+0.0012)
O═C′−O	122.1 (8)	122.5	122.4[f]	121.6 (−0.5)	121.8 (−0.3)	121.6 (−0.9)	121.6 (−0.8)
C_α−C′═O	126.7 (8)	126.1	125.8 (2)	126.6 (−0.1)	126.9 (+0.2)	126.9 (+0.8)	126.9 (+1.1)
O−C′−C_α	111.2 (8)	111.4	111.8 (1)	111.8 (+0.6)	111.3 (+0.1)	111.6 (+0.2)	111.6 (−0.2)
C′−C_α−C_β	112.8 (10)	112.4	112.7 (1)	113.0 (+0.2)	112.0 (−0.8)	111.7 (−0.7)	111.8 (−0.9)
C′−O−H		105.9	105.8 (2)	107.4	105.2	106.0 (+0.1)	106.2 (+0.4)
			exp (r_z)[e]	MM3 (r_g)[d]			MM4 (r_z)
I_a			8.2673	8.2924 (+0.35%)			8.2314 (−0.39%)
I_b			21.9810	22.1598 (+0.81%)			21.9232 (−0.26%)
I_c			29.1882	29.3818 (+0.67%)			29.2087 (+0.07%)
μ		1.850	1.550[e]	1.690 (+0.140)[d]			1.578 (+0.028)

[a] Bond lengths in Å; bond angles in degrees; moments of inertia in 10^{-39} g cm^2, and dipole moment in debye. [b] Reference 29. [c] Reference 30. [d] Reference 9. [e] Reference 31. [f] Calculated from the values of the other two angles (C_α−C′═O and O−C′−C_α).

TABLE 5: Structural Data from Experiment, MM3, and MM4 for Methyl Formate[a]



	exp (r_g)[b]	MP2/6-311++G(2d,2p)	exp (r_s)[c]	MM3 (r_g)[d]	MM4 (r_g)	MM4 (r_e)	MM4 (r_s)
C′═O	1.208 (5)	1.2080	1.200 (1)	1.2131 (+0.0051)	1.2119 (+0.0039)	1.2071 (−0.0009)	1.2083 (+0.0083)
C′−O	1.343 (7)	1.3432	1.334 (1)	1.3339 (−0.0091)	1.3460 (+0.0030)	1.3400 (−0.0032)	1.3419 (+0.0079)
C′−H	1.103	1.0916	1.101 (1)	1.1061 (+0.0031)	1.1026 (−0.0004)	1.0843 (−0.0073)	1.0866 (−0.0144)
O−C	1.447 (5)	1.4424	1.437 (1)	1.4401 (−0.0069)	1.4403 (−0.0067)	1.4340 (−0.0084)	1.4362 (−0.0008)
O═C′−O	126.8 (16)	125.5	125.8 (10)	125.5 (−1.3)	125.6 (−1.2)	124.7 (−0.8)	124.9 (−0.9)
O−C′−H	109.3	109.4	109.3 (10)	111.3 (+2.0)	109.7 (+0.4)	110.3 (+0.9)	110.2 (+0.9)
C′−O−C	114.3 (16)	114.0	114.8 (10)	115.7 (+1.4)	114.4 (+0.1)	114.7 (+0.7)	114.8 (+0.0)
			exp (r_z)[c]	MM3 (r_g)[d]			MM4 (r_z)
I_a			4.1990	4.2106 (+0.28%)			4.2124 (+0.32%)
I_b			12.1367	12.2924 (+1.28%)			12.1234 (−0.11%)
I_c			15.8208	15.9539 (+0.84%)			15.8138 (−0.04%)
μ		1.996	1.770[c]	1.830 (+0.060)[d]			1.786 (+0.016)

[a] Bond lengths in Å; bond angles in degrees; moments of inertia in 10^{-39} g cm^2, and dipole moment in debye. [b] Reference 32. [c] Reference 33. [d] Reference 9.

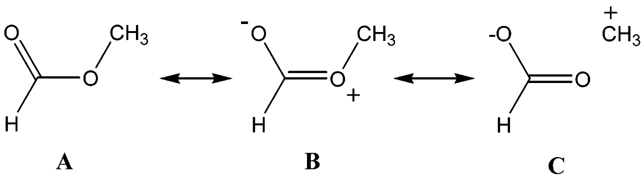
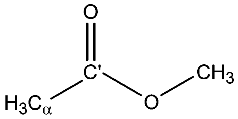


Figure 7. Resonance structures of methyl formate.

The electron-donating methyl group tends to lengthen the C′−O bond through the inductive effect. However, it also can shorten the C′−O through a resonance effect (hyperconjugation; see Figure 7). This competition between inductive and resonance effects can be seen almost everywhere (such as in the methylamine Bohlmann effect). For methyl formate, the resonance effect is much stronger than the inductive effect because of the presence of an electron-donating methyl group that significantly stabilizes resonance form B shown in Figure 7. Therefore, the C′−O bond is much shorter than that in formic acid, and the C═O bond is longer.

The inductive effect is not geometry-dependent. It is simply treated by the electronegativity effect. However, the resonance effect described here is dependent on the overlap of the nonbonded orbital (lone pair) on the oxygen and the π* orbital on the carbonyl carbon. It is dihedral angle-dependent, and it is treated by a torsion−stretch interaction in MM4. In general, the MM4 methyl formate structures are in agreement with experiment and with the QM results to within the experimental errors. The moments of inertia were also well fit to the microwave values. The energy difference between the E and Z conformers of methyl formate was reported to be 3.85(20) kcal/mol in favor of Z by Ruschin and Bauer[34] in 1980. In 1981, Blom and Gunthard[35] measured this energy as 4.75(19) kcal/mol in their IR matrix study. Table 2 shows that the high-level QM calculation gave this value as 4.94 kcal/mol, which is very

TABLE 6: Structural Data from Experiment, MM3, and MM4 for Methyl Acetate[a]



	exp (r_g)[b]	MP2/6-311++G(2d,2p)	exp (r_s)	MM3 (r_g)[c]	MM4 (r_g)	MM4 (r_e)	MM4 (r_s)
C′═O	1.209 (6)	1.2122		1.2147 (+0.0057)	1.2152 (+0.0062)	1.2106 (−0.0016)	1.2117
C′−O	1.360 (7)	1.3541		1.3584 (−0.0016)	1.3518 (−0.0082)	1.3451 (−0.0090)	1.3473
C′−C$_\alpha$	1.496 (7)	1.5024		1.4919 (−0.0041)	1.5061 (+0.0101)	1.4988 (−0.0036)	1.5012
O−C	1.442 (7)	1.4394		1.4399 (−0.0021)	1.4431 (+0.0011)	1.4368 (−0.0026)	1.4379
O═C′−O	123.0	123.3		123.1 (+0.1)	123.7 (+0.7)	123.3 (+0.0)	123.4
O−C′−C$_\alpha$	111.4	110.8		111.5 (+0.1)	110.6 (−0.8)	110.8 (+0.0)	110.9
C′−O−C	116.4	114.0		115.8 (−0.6)	114.8 (−1.6)	115.0 (+1.0)	115.2
C$_\alpha$−C′═O	125.6	125.9		125.4 (−0.2)	125.7 (+0.1)	125.9 (+0.0)	125.8
			exp (r_z)[d]	MM3 (r_g)[c]			MM4 (r_z)
I_a			8.1901	8.2313 (+0.50%)			8.2164 (+0.32%)
I_b			20.1236	20.4254 (+1.50%)			20.0637 (−0.30%)
I_c			27.2778	27.5668 (+1.06%)			27.2979 (+0.07%)
μ		2.032	1.690[e]	1.780 (+0.090)[c]			1.724 (+0.034)

[a] Bond lengths in Å; bond angles in degrees; moments of inertia in 10^{-39} g cm^2, and dipole moment in debye. [b] Reference 36. [c] Reference 9. [d] Reference 37. [e] Reference 48.

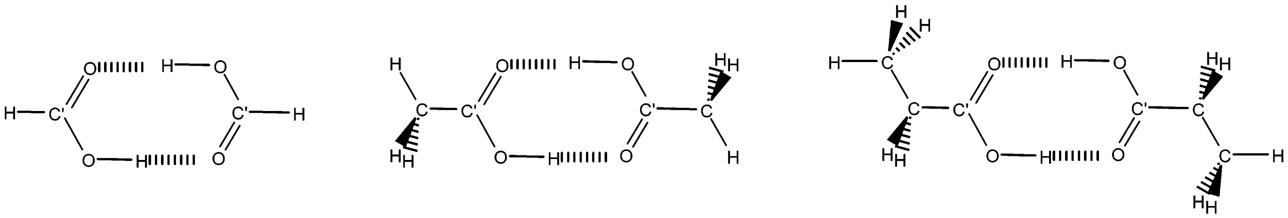
close to Blom and Gunthard's value. Therefore, the MM4 value (4.77 kcal/mol) was fit to Blom and Gunthard's value. The MM4 Z → E and E → Z rotational barriers were also fit to the QM results. The slightly higher equilibrium energy and rotational barriers in methyl formate compared to those in formic acid also suggest that the resonance effect is stronger in methyl formate. The rotational barrier for the methoxyl group was reported to be 1.19(4) kcal/mol by Curl[33] in his microwave study. The MM4 and QM calculations gave this barrier as 1.17 and 0.78 kcal/mol, respectively.

Methyl Acetate. This is a key compound in the studies of esters and lactones because it shares many common parameters with larger esters and lactones. A gas-phase electron diffraction r_g structure for methyl acetate was reported by Pyckhout et al.[36] in 1986. A microwave determination of the moments of inertia was reported by Sheridan et al.[37] in 1980. However, no experimental r_s structure for this compound has been reported. Table 6 summarizes these experimental data, together with the QM and MM4 results for methyl acetate. We also observe here that the C′−O bond in methyl acetate is shorter than in its acid counterpart, although the shortening effect is less pronounced than that in the formates. The reduced shortening effect here can be explained by the countereffect of the methyl group attached to the carbonyl carbon C′, which tends to lengthen the C′−O bond instead. All MM4 structures were fit to the experimental and QM values to within the experimental errors, except the r_g value of the C′−O−C angle. Compared to the GED value, the MM4 calculated value was 2° too small for this angle. However ,the smaller value for this angle in the MM4 calculation is required to fit the moments of inertia (see Table 6). Compared to the MM3 calculation, in which we tried to fit the r_g C′−O−C angle more accurately, MM4 now gives much better moments of inertia. The resolution of the heavy-atom bond angles in the GED experiment is just not very good because of the planar trigonal nature of the system. The high-level QM calculation also shows that the C′−O−C angle should not be very big. In 1981, Blom and Gunthard[35] reported a value of 8.5(10) kcal/mol for the Z ⇄ E equilibrium energy from their IR matrix study. This large energy difference between the two conformers was confirmed by our QM study. According to the later, the Z → E rotational barrier for methyl acetate is very similar to that for methyl formate (13.12 vs 13.52 kcal/mol). However, the Z ⇄ E equilibrium energy is much larger (7.54 vs 4.94 kcal/mol), and the E → Z rotational barrier is much lower for methyl acetate (5.57 vs 8.58 kcal/mol) (see Table 2). These differences are due to the steric effect in the E conformer. MM4 gave values of 7.53, 13.32, and 5.79 kcal/mol for the Z ⇄ E equilibrium energy and the Z → E and E → Z rotational barriers, respectively. In 1980, Sheridan and co-workers[37] reported internal rotational barriers for the methyl and methoxyl groups of methyl acetate in their microwave study. They were determined to be 0.285(1) and 1.217(8) kcal/mol, respectively. The MM4 and QM results for these two barriers are 0.278 and 1.186 kcal/mol and 0.210 and 0.838 kcal/mol, respectively.

Formic, Acetic, and Propionic Acid Dimers. Carboxylic acids usually form stable dimers in the gas phase because of the strong hydrogen bonding between carboxylic hydrogen and carbonyl oxygen. The dimerization energies for formic, acetic, and propionic acids were reported to be −14.1(15), −14.2(7), and −14.5(12) kcal/mol, respectively, by Mathews and Sheet[38] in 1969 in their temperature dependence of gas volume measurement. In 1987, Henderson[39] determined the heat of dimerization for formic acid as −11.69 kcal/mol by FTIR measurements. The FTIR method might be expected to give a better result because the gas-volume method might yield other associations beside dimer formation. However, the high-level QM calculations carried out by Tsuzuki et al.[40] suggest that the dimerization energy of the formic acid dimer is close to the gas-volume values. The energies were calculated to be −13.54 kcal/mol at the MP2/cc-pV5Z level and −13.93 kcal/mol with CCSD(T) theory at the basis set limit. MM4 calculations give values of −12.54, −13.25, and −13.33 kcal/mol for formic, acetic, and propionic acids, respectively. The structures and dimerization energies of carboxylic acid dimers are summarized in Table 7.

Although the geometries and conformational energies for simple acids and esters are much improved with the MM4 force field, we would like to determine if MM4 is indeed better than other force fields besides MM3. The MMFF94[41] force field was chosen for comparison because it has recently been widely accepted. In Table 8, we compare high-level QM, MM4, and MMFF94 geometries and conformational energies for five selected acids and esters. The Table clearly shows that the MM4 results are in better agreement.

TABLE 7: Structural Data and Energies of Dimerization from Experiment, QM, MM3, and MM4 for Formic, Acetic, and Propionic Acid Dimers[a]



	exp	B3LYP/6-311++G(2d,2p)	MM3 (R_g)	MM4 (R_e)
		Formic Acid		
C...C		3.802	3.911	3.857
O...O		2.672	2.733	2.672
O...H		1.671	1.751	1.703
<O...O−H		0.7	2.6	4.4
E_{dimer}	14.1(1.5)[b],11.69[c]	13.54(0.38)[d], 13.93[d] 14.56(0.63)[e]	12.18	12.54
		Acetic Acid		
C...C		3.850	3.961	3.895
O...O		2.662	2.733	2.671
O...H		1.662	1.751	1.704
<O...O−H		0.5	2.0	5.6
E_{dimer}	14.2(0.7)[b]	14.98(0.60)[e]	12.14	13.25
		Propionic Acid		
C...C		3.857	3.964	3.912
O...O		2.668	2.733	2.670
O...H		1.669	1.751	1.704
<O...O−H		0.4	2.0	5.8
E_{dimer}	14.5(1.2)[b]	14.59(0.77)[e]	12.22	13.33

[a] All distances are in Å; all angles are in degrees; E_{dimer} values are in kcal/mol. [b] Reference 38. [c] Reference 39. [d] Reference 40. MP2/cc-pV5Z and CCSD(T) (limit) values. The geometries of the monomers were frozen during dimer optimization.The value in parentheses is the BSSE value. [e] This work. B3LYP/6-311++G(2d,2p) value; fully optimized.The values in parentheses are BSSE values.

Moments of Inertia and Dipole Moments. The moments of inertia and dipole moments of carboxylic acids and esters were improved significantly from those of the previous MM3 calculations.[9] The improvement in the moments of inertia is mainly due to the introduction of torsion−bend cross terms and a new carbonyl carbon atom type (157) for formic acid and formates. Table 9 shows that the overall rms errors for 36 moments of inertia are 1.27% (r_g values) and 0.32% (r_z values) from MM3 and MM4 calculations, respectively. The largest improvements are in those three conformers that were not studied by MM3. They are (*E*)-formic acid and *trans*-ethyl formate, and *gauche*-ethyl formate. MM3 cannot provide a good fit for both (*Z*)-formic acid and (*E*)-formic acid at the same time because of the lack of torsion−bend interactions in the MM3 force field. In general, the MM4 moment of inertia calculations are in good agreement with the microwave results.[21,23,28,31,33,37,42,43] However, the calculated results for a few moments , especially those of *trans*-ethyl formate,[42] δ-valerolactone (boat),[44] and ϵ-caprolactone,[45] were not as good. The I_a moment of *trans*-ethyl formate cannot be improved further because the compound shares common O−C−C (type 75−1−1) bending and torsion−bend parameters with gauche-ethyl formate and lactones. The I_c moments of d-valerolactone (boat) and e-caprolactone might be improved by fine tuning the C−O−C−C (type 3−75−1−1) and O−C−C−C (type 75−1−1−1) torsional parameters. However, this improvement could not be carried out without jeopardizing other moments of inertia of *gauche*-ethyl formate and lactones that are already in good agreement with experiment.

The improvement of the structures of the acids and esters is part of the reason that the MM4 dipole moment calculations are improved. However, the incorporation of induced dipole moments into the MM4 force field[46] is a more important reason. Table 10 summarizes the experimental dipole moments along with the MM3 and MM4 results. All MM4 dipole moments for carboxylic acids and esters are in fair agreement with experiment,[23,28,31,33,42,43,47−49] except that for ϵ-caprolactone (chair).[49] The problem here is probably the experimental value, which was determined by polarization methods in solution. The MM4 dipole moment rms error calculated from the microwave (Stark effect) values is improved from that of the MM3 from 0.135 to 0.024 D.

Vibrational Frequencies. The MM4 vibrational frequencies for acids and esters are in satisfactory agreement with experimental IR spectra.[50−54] They are improved significantly from those of the MM3 calculations (rms error of 30 cm^{-1}),[9] with a rms error of 19 cm^{-1} for 74 frequencies of 5 compounds. Tables 2S−6S (Supporting Information) summarize the experimental and MM4 frequencies along with the vibrational symmetry assignments for formic acid, acetic acid, methyl formate, methyl acetate, and γ-butyrolactone.

Although the C′═O bonds in the acids and esters have an −OH (or −OR) electron-withdrawing group attached, we found that their bond lengths are not much different from those in their aldehyde and ketone counterparts. This is because the bond shortening from the electronegativity effect of the hydroxyl or alkoxyl oxygen and the bond lengthening from the resonance effect of the O═C′−O partially cancel each other out. However, the experiments show that C′═O stretching frequencies are ~30−60 cm^{-1} higher in the acids and esters than in the aldehydes and ketones. The reason for this difference is not that the C′═O bond becomes stronger but rather that a strong C′═O /C′−O stretch−stretch coupling exists in the acids and esters because of their similar reduced mass and vibrational symmetries (both are A′). As a result, the coupling pushes the C′═O frequency higher and the C′−O frequency lower. This conclusion was confirmed by our QM results. In the analysis

TABLE 8: Comparison of Structures Determined from Quantum Mechanics, MM4, and MMFF94 and Conformational Energies for Selected Acids and Esters[a]

	exp [ref]	MP2/ 6-311++G(2d,2p)	MM4 (r_e)	MMFF94[41]
		(*Z*)-Formic Acid		
C′═O		1.2052	1.2005	1.2165
C′−O		1.3498	1.3466	1.3417
O−H		0.9674	0.9671	0.9802
O═C′−O		125.0	123.8	121.8
C′−O−H		106.7	106.8	104.3
		(*E*)-Formic Acid		
C′═O		1.1985	1.1938	1.2172
C′−O		1.3570	1.3465	1.3417
O−H		0.9624	0.9614	0.9761
O═C′−O		122.4	121.9	124.3
C′−O−H		108.8	109.5	112.0
ΔE_{E-Z}	3.900(85) [23]	4.160[b]	3.904	4.895
		Acetic Acid		
C′═O		1.2101	1.2089	1.2188
C′−O		1.3607	1.3517	1.3458
$C'-C_\alpha$		1.5000	1.4953	1.4928
O−H		0.9666	0.9668	0.9802
O═C′−O		122.5	122.3	121.0
$O-C'-C_\alpha$		111.3	112	112.4
C′−O−H		106.0	106.2	104.1
ΔE_{E-Z}		5.333[b]	5.347	5.872
		Methyl Formate		
C′═O		1.2080	1.2071	1.2202
C′−O		1.3432	1.3400	1.3559
O−C		1.4424	1.4340	1.4280
O═C′−O		125.5	124.7	126.7
C′−O−C		114.0	114.7	113.8
ΔE_{E-Z}	4.75(19) [35]	4.940[b]	4.773	5.275
		Methyl Acetate		
C′═O		1.2122	1.2106	1.2227
C′−O		1.3541	1.3451	1.3612
$C'-C_\alpha$		1.5024	1.4988	1.4980
O−C		1.4394	1.4368	1.4281
O═C′−O		123.3	123.3	125.6
$O-C'-C_\alpha$		110.8	110.8	110.0
C′−O−C		114.0	115	113.9
ΔE_{E-Z}	8.5(10) [35]	7.541[b]	7.526	9.691

[a] Bond lengths in Å; bond angles in degrees; energy in kcal/mol. [b] Conformational energies are calculated at the Becke3LYP/6-311++G(2d,2p) level of theory.

TABLE 9: Comparative Results of Moments of Inertia for Selected Acids, Esters, and Lactones[a]

	exp	ref	MM3	error (%)	MM4	error (%)
			(*Z*)-Formic Acid			
I_a	1.0965	21	1.1089	1.13	1.0992	0.25
I_b	6.9610		6.9014	−0.86	6.9774	0.24
I_c	8.0575		8.0103	−0.59	8.0691	0.14
			(*E*)-Formic Acid			
I_a	0.9706	23	0.9409	−3.06	0.9724	0.19
I_b	7.1794		7.3173	1.92	7.1908	0.16
I_c	8.1604		8.2582	1.20	8.1561	−0.05
			Acetic Acid			
I_a	7.4034	28	7.4542	0.69	7.4069	0.05
I_b	8.8537		8.9172	0.72	8.8766	0.26
I_c	15.7598		15.8333	0.47	15.7861	0.17
			Propionic Acid			
I_a	8.2637	31	8.2924	0.35	8.2314	−0.39
I_b	21.9810		22.1598	0.81	21.9232	−0.26
I_c	29.1882		29.3818	0.66	29.2087	0.07
			Methyl Formate			
I_a	4.1990	33	4.2106	0.28	4.2124	0.32
I_b	12.1367		12.2924	1.28	12.1234	−0.11
I_c	15.8208		15.9539	0.84	15.8138	−0.04
			Methyl Acetate			
I_a	8.1901	37	8.2313	0.50	8.2164	0.32
I_b	20.1236		20.4254	1.50	20.0637	−0.30
I_c	27.2778		27.5668	1.06	27.2979	0.07
			trans-Ethyl Formate			
I_a	4.7288	42	4.7369	0.17	4.6895	−0.83
I_b	28.8911		29.2536	1.25	28.7738	−0.41
I_c	32.5384		32.9121	1.15	32.5145	−0.07
			gauche-Ethyl Formate			
I_a	8.4044	42	8.7256	3.82	8.4374	0.39
I_b	21.8574		21.2371	−2.84	21.8777	0.09
I_c	26.1197		25.8135	−1.17	26.0106	−0.42
			γ-Butyrolactone			
I_a	11.5300	43	11.5600	0.26	11.5487	0.16
I_b	23.4100		23.5500	0.60	23.4980	0.38
I_c	32.7500		32.9600	0.64	32.8439	0.29
			δ-Valerolactone (Half-Chair)			
I_a	18.0040	44	17.9030	−0.56	17.9954	−0.05
I_b	32.8000		33.3210	1.59	32.8610	0.19
I_c	47.3820		47.7130	0.70	47.5165	0.28
			δ-Valerolactone (Boat)			
I_a	18.4560	44	18.5444	0.48	18.4434	−0.07
I_b	32.3290		32.5352	0.64	32.2834	−0.14
I_c	44.9290		45.1899	0.58	45.2733	0.77
			ϵ-Caprolactone (Chair)			
I_a	26.2200	45	26.2100	−0.04	26.1353	−0.32
I_b	43.7000		43.8900	0.43	43.5702	−0.30
I_c	62.2200		61.9000	−0.51	61.7721	−0.72
				rms 1.27		rms 0.32

[a] All moments of inertia are given in units of 10^{-39} g cm^2.

of the internal coordinate force-constant matrix from the Becke3LYP/6-31G** calculations, we found that the force constants for the C′═O bond stretch in formaldehyde and formic acid are almost identical (14.02 vs 13.98 mdyn/Å without scaling). However, the coupling force constant between the C′═O and C′−O bonds is significant (∼1.3 mdyn/Å) in formic acid. The infrared spectrum shows that the C′═O frequencies are 1744 and 1770 cm^{-1} for formaldehyde[5] and formic acid,[50] respectively. The C′═O frequency is even higher in acetic acid (1799 cm^{-1})[51] because of additional coupling between the C′═O and $C'-C_\alpha$ bonds.[55] The C′═O frequencies of methyl formate and acetate are lower than those of their acid counterparts by 16 and 28 cm^{-1}, respectively because both resonance and inductive effects from methoxyl groups favor longer and weaker C′═O bonds for esters. They are reported to be 1754 and 1771 cm^{-1} experimentally for methyl formate and acetate, respectively. Assignments of the C′−O stretching frequencies are very difficult to make because the C′−O bond stretching is strongly coupled to other modes. Basically, the frequencies range from 950 to 1100 cm^{-1} and 1200 to 1250 cm^{-1} for acids and esters, respectively. The higher C′−O frequencies in esters are due to the stronger O═C′−O resonance, as we discussed previously, and the coupling between the C′−O and $O-C_{sp3}$ bonds. The C′−H frequencies for formic acid and formates (exp ∼2930−2950 cm^{-1}) are much higher than those for aldehydes (exp ∼2800−2830 cm^{-1}) because of the electronegative group (hydroxyl or alkoxyl) attached to the acid and esters. The electronegative substituent leads to a shorting of the C−H bond, which in term leads to the higher stretching frequency.[56] The MM4-calculated C′−H frequencies are 2950 and 2955 cm^{-1} for formic acid and methyl formate, respectively. Although both the C′−O−H and C′−O−C bending modes are strongly coupled to other stretching and bending modes, they are not too difficult to distinguish. The experimental and MM4 C′−O−H bending frequencies are 1229 and 1233 cm^{-1}, respectively, for formic acid and 1280 and 1287 cm^{-1}, respectively, for acetic acid. The corresponding experimental and MM4 C′−O−C bending fre-

TABLE 10: Comparative Results of Dipole Moments for Selected Acids, Esters and Lactones[a]

	method[b]	exp	ref	MM3	error	MM4	error
(*Z*)-formic acid	MW-S	1.420	47	1.730	0.310	1.443	0.023
(*E*)-formic acid	MW-S	3.790	23	3.890	0.100	3.769	−0.021
acetic acid	MW-S	1.700	28	1.690	−0.010	1.673	−0.027
propionic acid	MW-S	1.550	31	1.690	0.140	1.578	0.028
methyl formate	MW-S	1.770	33	1.830	0.060	1.786	0.016
methyl acetate	MW-S	1.690	48	1.780	0.090	1.724	0.034
trans-ethyl formate	MW−S	1.980	42	1.830	−0.150	1.979	−0.001
gauche-ethyl formate	MW-S	1.810	42	1.870	0.060	1.781	−0.029
γ-butyrolactone (envelope)	MW-S	4.270	43	4.230	−0.040	4.287	0.017
δ-valerolactone (half-chair)	in benzene	4.220	49	4.270	0.050	4.233	0.013
δ-valerolactone (boat)	in benzene	4.220	49	4.340	0.120	4.231	0.011
ϵ-caprolactone (chair)	in benzene	4.450	49	4.300	−0.150	4.184	−0.266
					rms[c] 0.135		rms[c] 0.024

[a] All dipole moments are in debye. [b] MW-S indicates microwave (Stark effect) values. [c] The rms error is calculated from the microwave data only because the other data are typically less accurate.

quencies are 325 and 310 cm^{-1}, respectively, for methyl formate and 302 and 327 cm^{-1}, respectively, for methyl acetate.

Heats of Formation. The heat of formation is one of the most important characteristics of a compound available to the chemist. The calculated value is also a good indicator of the quality of the force field. If a force field cannot be used to calculate heats of formation with experimental accuracy, it probably contains serious hidden errors. Therefore, it was our goal to fit the calculated heats of formation for a wide range of compounds to the experimental values as best we could. Traditionally, the heats of formation have been calculated by the increment addition scheme. In the MM2 and MM3 force fields, these increments are the contributions from the formation of bonds (bond enthalpies), the effects of strain energy as represented by steric energy, and the structural enthalpies. The structural enthalpies were necessary for averting the problem of nontransferability of bond enthalpies alone. Although the standard scheme used in MM2,[57] MM3,[58] and ab initio[59] methods works reasonably well in the heats of formation calculation, the proper procedure should also include all of the statistical mechanical energies[60] (i.e., the zero-point energies (ZPE) and thermal heat contents). However, the accuracy of the statistical mechanical energies depends on an accurate calculation of the vibrational levels (at least the low-lying ones). Because the MM4 frequency calculations were significantly improved from the previous force-field calculations, the MM4 default heat-of-formation calculation now includes all of the statistical mechanical energy terms.[1] In the MM4 heat-of-formation calculation, the following equation is used:

$$\Delta H_f^\circ = \mathrm{BE} + \mathrm{SE} + \mathrm{MH} + \mathrm{POP} + \mathrm{TORS} - H_{\mathrm{atom}}$$

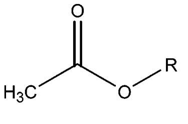
BE is the bond enthalpy, SE is the structural enthalpy, and MH is the molar heat content (including zero-point, thermal, translation/rotational, and PV term energies). POP is the contribution from higher-energy conformations, TORS is the contribution from the vibrations involving very low torsion frequencies, and H_{atom} is the heat of atomization of the elements. The programmed value of TORS is 0.0 kcal/mol for rigid system, and 0.5715 kcal/mol is added for each torsion with a low torsional barrier (<5 kcal/mol).

The parameters required for the heat-of-formation calculation on carboxylic acids and esters have been evaluated by a least-squares fitting of the MM4 data to the experimental values. The optimized parameters and the input data for the heat-of-formation calculation are listed in the Table 11 and Table 7S (Supporting Information), respectively. The calculated and experimental heats of formation[61−65] for selected acids, esters, and lactones are summarized in Table 12. Those experimental values with reported errors of >1.0 kcal/mol were not considered reliable and were excluded from weighting the least-squares fitting. The standard deviation of the MM4 heats of formation was 0.67 kcal/mol for 30 selected compounds. Although the result is much improved from the MM3 calculation value (1.14 kcal/mol), the error is still higher than the reported experimental error (av ±0.44 kcal/mol). The significance of this fact is uncertain.

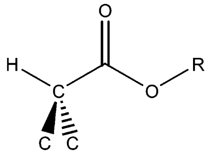
TABLE 11: MM4 Heats of Formation Parameters for Acids, Esters, and Lactones[a]

bond/structural increment	heat parameter
C′═O	−202.5000
C′−O	−111.8574
O−H	−113.2656
O−C	−91.0420
H−C′═O (acid)	6.3690
H−C′═O (ester)	9.3602
C′−Me	−2.6297
C′−Sec	3.3924
C′−Ter	5.1516
O−Me	3.3252
O−Sec	−3.2637
O−Ter	−5.9224
TORS	0.5715

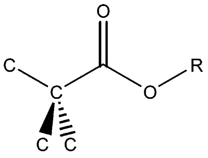
[a] All values are in kcal/mol.



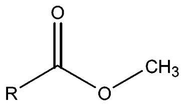
C'-Me



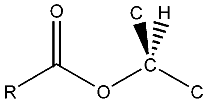
C'-Sec



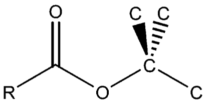
C'-Ter



O-Me



O-Sec



O-Ter

MM4 Results for Nonanolactone and Tridecanolactone Crystal Structures. The performance of the force field for the condensed-phase calculations is always of concern. On the basis of what we have learned from our previous studies, if the force field was reasonable enough and the proper approximations were applied, then the results for condensed-phase calculations are usually reasonably good.[66] To determine how well the MM4 force field predicts the experimental structures in the condensed phase, we have examined the 5 lowest-energy conformations of nonanolactone and the 10 lowest-energy conformations of

TABLE 12: Calculated and Experimental Heats of Formation for Acids, Esters, and Lactones[a,b]

eq	wt	ΔH_f° (MM4)	ΔH_f° (exp)[c]	$\Delta\Delta H_f^\circ$ (MM4 − exp)	compound
1	5	−90.57	−90.57	0.00	formic acid
2	10	−103.01	−103.26	0.25	acetic acid
3	8	−107.78	−108.40	0.62	propionic acid
4	5	−112.84	−112.40	−0.44	*n*-butyric acid
5	5	−118.02	−117.15	−0.87	valeric acid
6	0	−120.11	−122.00[d]	1.89	isovaleric acid
7	0	−122.72	−117.54[d]	−5.18	pivalic acid
8	5	−123.06	−122.70	−0.36	caproic acid
9	4	−128.39	−127.70	−0.69	heptanoic acid
10	4	−133.47	−132.70	−0.77	octanoic acid
11	5	−133.85	−133.85[d]	0.00	2-ethexanoic acid
12	5	−85.05	−85.05[d]	0.00	methyl formate
13	0	−106.64	−109.18[e]	2.54	*tert*-butyl formate
14	10	−98.22	−98.54[d]	0.32	methyl acetate
15	10	−106.17	−106.34	0.17	ethyl acetate
16	10	−115.32	−115.12	−0.20	*i*-propyl acetate
17	10	−116.64	−116.10	−0.54	*n*-butyl acetate
18	10	−123.45	−123.45[f]	0.00	*tert*-butyl acetate
19	8	−111.00	−111.00[d]	0.00	ethyl propionate
20	0	−113.90	−117.70	3.80	methyl α-methylbutyrate
21	0	−121.63	−124.90	3.27	ethyl α-methylbutyrate
22	0	−129.69	−130.30	0.61	*s*-butyl butyrate
23	4	−121.22	−121.20	−0.02	ethyl pentanoate
24	4	−126.82	−127.50	0.68	*n*-propyl pentanoate
25	6	−130.63	−130.20	−0.43	*i*-propyl pentanoate
26	2	−132.12	−133.90	1.78	*n*-butyl pentanoate
27	4	−134.79	−137.00	2.21	*s*-butyl pentanoate
28	3	−134.02	−135.90	1.88	*i*-butyl pentanoate
29	5	−113.27	−112.70	−0.57	methyl valerate
30	0	−115.35	−119.00	3.65	methyl isovalerate
31	0	−123.10	−126.00	2.90	ethyl isovalerate
32	7	−118.25	−118.25[d]	0.00	methyl pivalate
33	0	−126.32	−128.10	1.78	ethyl pivalate
34	5	−118.57	−118.00	−0.57	methyl caproate
35	5	−123.65	−123.50	−0.15	methyl heptanoate
36	5	−86.41	−87.00[g]	0.59	γ-butyrolactone
37	5	−89.32	−89.90[g]	0.58	δ-valerolactone
38	5	−96.42	−94.70[g]	−1.72	ϵ-caprolactone
39	5	−97.62	−98.30[g]	0.68	heptanlactone

[a] Standard deviation = 0.8182 based on 30 equations. Weighted standard deviation = 0.6744 based on 30 equations. [b] All values are in kcal/mol. [c] All experimental values are from ref 61 except where otherwise noted. [d] Reference 62. [e] Reference 63. [f] Reference 64. [g] Reference 65.

tridecanolactone in the isolated environment (gas phase). As we expect, the lowest-energy conformations for both nonanolactone and tridecanolactone (see Figures 8 and 9) found in the gas phase by MM4 are also found in the X-ray crystal structures reported by Wiberg and co-workers.[67] Both lowest-energy conformations were then further optimized in the crystalline environment using the procedure described in our previous studies of cyclic peptides.[66] The MM4 results along with the experimental and MM3 results for several ester group-related geometric parameters of nonanolactone and tridecanolactone are summarized in Table 13. As one can see from the Table, both the MM3 and the MM4 optimized structures of nonanolactone and tridecanolactone are in close agreement with the reported X-ray structures.

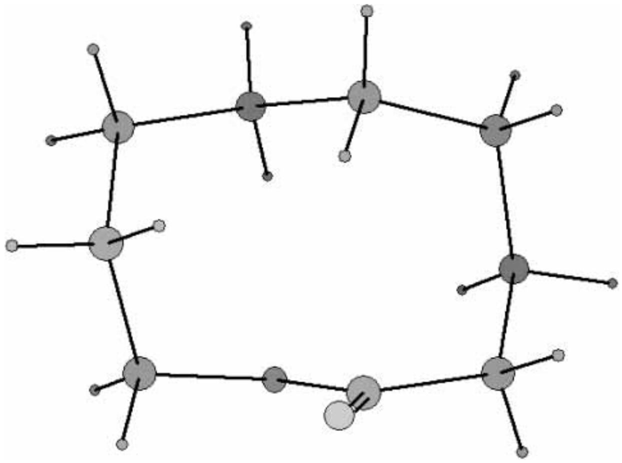


Figure 8. MM4 lowest-energy conformation of nonanolactone.

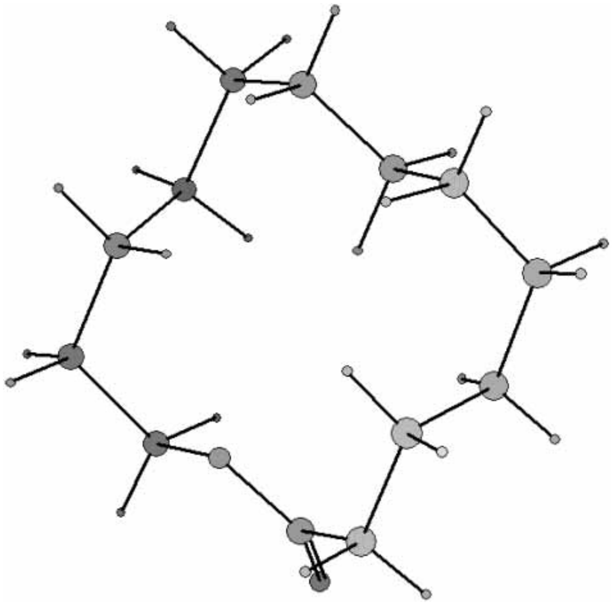


Figure 9. MM4 lowest-energy conformation of tridecanolactone.

TABLE 13: Structural Data from Experiment, MM3 and MM4 for 10- and 14- Membered Ring Lactone Crystals[a]

	nonaolactone			tridecanolactone		
parameter	crystal[b]	MM3[c]	MM4[c]	crystal[b]	MM3[c]	MM4[c]
C′═O	1.199	1.214	1.216	1.202	1.214	1.216
C′−O	1.339	1.360	1.355	1.333	1.362	1.355
C_α−C′−O	111.4	112.2	111.5	112.8	112.0	111.5
C′−O−C	117.2	117.3	117.2	116.2	116.1	115.8
O−C−C	112.2	111.6	111.7	108.1	109.7	108.9
O═C′−O	123.9	123.2	123.5	122.1	123.1	123.3
O═C′−C_α	124.7	124.6	124.9	125.2	124.9	125.2
C_β−C_α−C′−O	38.1	36.6	35.4	−56.0	−53.9	−67.4
C_α−C′−O−C	−169.5	−170.3	−171.4	−179.8	−179.1	−176.7
C′−O−C−C	75.8	73.6	74.1	−179.0	177.3	−170.8
O−C−C−C	61.9	63.7	63.2	62.0	59.4	61.2

[a] All bond lengths are in Å, and all bond angles and torsional angles are in degrees. [b] Reference 67. [c] Both MM3 and MM4 structures are minimized in the crystal lattice with a dielectric constant of 4.0 using the procedure described in ref 66.

Concluding Remarks

Generally speaking, the overall results of MM4 calculations for carboxylic acids and esters were much improved from those of MM3 calculations. The improvements are mainly due to the introduction of more cross terms in the force-constant matrix (such as torsion−bend, bend−torsion−bend) and a new carbonyl carbon atom type (157) for formic acid and formates. In this study, we found that we usually can fit both ab intio MP2/6-311++G(2d,2p) r_e structures and experimental moments of inertia (r_z structures) well at the same time. This give us some confidence in the use of the MP2/6-311++G(2d,2p) structures for future force-field studies. The conformational energies and rotational barriers calculated by the Becke3LYP/6-311++G(2d,2p) theory also gave very good results compared to the experimental values. As computing facilities become more powerful, these two levels of theory will probably be the standards for future force-field development (at least for now). Finally, the success of the condensed-phase calculations (nonanolactone and tridecanolactone X-ray crystal structures) when we used the parameter set derived from the gas phase also confirms our previous findings. If the force field derived from the gas phase is reasonable enough and if proper procedures are subsequently applied, the results for condensed-phase calculations are usually good.

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Supporting Information Available: Experimental and MM4 frequencies and vibrational symmetry assignments and parameters for heat-of-formation calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) The specific theory and basis set, Becke3LYP/6-31G**, chosen in the frequency calculations, is due to the fact that the most available scaling factors published by Pulay were done with this level of theory.

(17) FSCALE, written by the author, is an ab initio force constant scaling procedure using the algorithm suggested by Pulay. Currently, the FSCALE program uses the force constant matrix and Cartesian coordinates generated by the Gaussian program (stored in a Gaussian checkpoint, *.fchk, file in ASCII format) and the internal coordinates (with the scaling factors provided by the user) as inputs. The program scales and diagonalizes the force constant matrix and then calculates the frequencies.

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