Molecular Mechanics Calculations on Carbonyl Compounds. IV. Heats of Formation

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Dedicated to Professor Paul von R. Schleyer

ABSTRACT: Molecular mechanics (MM4) calculations on the heats of formation of aldehydes and ketones were carried out for a total of 59 compounds (10 aldehydes and 49 ketones). Optimization of the heat of formation parameters was obtained by a least squares fit to the experimentally known heats of formation. With the optimized MM4 heat of formation parameters, the MM4 calculated heats of formation showed significant improvement over those of MM3. The standard and weighted root mean square deviations for the MM4 values were 0.35 and 0.31 kcal mol^{-1}, respectively, whereas for the MM3 values they were 0.42 and 0.39 kcal mol^{-1}, respectively. J Comput Chem 22: 1476–1483, 2001

Keywords: molecular mechanics (MM4) calculations; carbonyl compounds; heats of formation

Introduction

The heat of formation is a fundamental physical property of a molecule. Moreover, it might be argued that for molecular modeling and conformational analysis, this is the most important single property of the molecule. The development of theories of stereochemistry and molecular force fields has been greatly influenced by the experimental heats of formation. The standard heat of formation (ΔH_f) of a compound is defined as the enthalpy of its formation from its composing elements in their reference states at 25°C and 1 atm. The reference state of an element is its most stable state at the specified temperature and pressure. By definition, the enthalpies of formation of elements in their standard states are zero. For hydrocarbons, the heat of formation is the enthalpy of the following generic reaction:

$$m\text{C (graphite)} + \frac{n}{2}\text{H}_2 \rightarrow \text{C}_m\text{H}_n \qquad (1)$$

For aldehydes and ketones, the reaction is

$$(m+1)\text{C (graphite)} + \frac{n}{2}\text{H}_2 + \frac{1}{2}\text{O}_2 \rightarrow \text{C}_{m+1}\text{H}_n\text{O} \qquad (2)$$

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In molecular mechanics, one can calculate the energy of a compound with respect to the energy of the molecule at the bottom of the potential well (equilibrium energy). This energy is the internal steric energy determined by the force field equation. For calculations on the heat of formation, however, knowledge of more than just the minimum steric energy at the bottom of the potential well is required. In general, the heat of formation of a compound is determined by the sum total of contributions arising from the formation of bonds, the steric energy, and contributions from the statistical thermodynamics of the molecule. The latter is determined in part by the populations of the vibrational levels and the different conformers. In the MM3 and MM4 versions[1] of molecular mechanics, these concepts are incorporated into formula Eq. (3). Let us consider the calculation of the heat of formation for a single conformer of a molecule:

$$\Delta H_{f,i} = \sum_j (\mathrm{BE})_j + \sum_j (\mathrm{ST})_j + (\mathrm{SE})_i + (\mathrm{PFC})_i - \Delta H_{\mathrm{atom}} \quad (3)$$

where $\Delta H_{f,i}$ is the heat of formation for conformer i, BE is the bond enthalpy parameter, ST is the structural enthalpy parameter, $(\mathrm{SE})_i$ is the steric energy of conformer i of the compound, $(\mathrm{PFC})_i$ is the partition function contribution for conformer i, and ΔH_{atom} is the heat of formation of elements in the standard state from atoms. These terms are described in detail in several articles.[2–7, 30]

Compounds for Heat of Formation Calculations

A total of 53 different aldehyde and ketone compounds with experimentally known heats of formation were chosen for heat of formation parameterization in MM4. These were the same compounds used in the MM3 parameterization.[8] There were 10 different aldehydes and 42 different ketones. They ranged in complexity from small open-chain molecules like acetone to large fused-ring structures like diadamantanone. The bond and structural enthalpy parameters associated with the carbonyl group were adjusted in such a way that the calculated heats of formation agreed as closely as possible with the corresponding experimental heats of formation. Together these compounds covered the greatest number and variety of bond and structural enthalpy parameters for carbonyl compounds.

The bond and structural enthalpy parameters are listed according to number and type in Table I. The listed structural enthalpy parameters (see Fig. 1) are defined as follows: ME′ is the methyl group directly attached to a carbonyl, SEC′ is the structural unit in which two alkyl groups are attached to an α-carbon, TERT′ is the structural unit in which three alkyl groups are attached to the α-carbon, ISO′ is the structural unit in which two alkyl groups are attached to the β-carbon, NEO′ is the structural unit in which three alkyl groups are attached to the β-carbon; R5 is the five-membered ring (fixed value), R6 is the six- and higher membered ring (fixed value), and TOR is the enthalpy contribution from the population of torsional energy levels for each conformer (fixed value).

Those parameters involving the hydrocarbon part of the molecule are not listed, because they were already set in MM4.[9] The TOR term[2] applies for each bond involving heavy atom torsion. Therefore, 2-butanone has one TOR term, 2-pentanone has two, 2-hexanone has three, and so forth. The TOR term is needed because, although the harmonic approximation gives sufficiently good frequencies to calculate the thermodynamic properties of the molecule for the most part, for very low torsional frequencies the vibrational levels are more closely spaced and the enthalpy is noticeably higher than what would be calculated by the harmonic approximation alone. The TOR term is a correction added to the calculation to improve the enthalpy values.[2, 6] Because different atom types are assigned for the carbonyl carbon in aldehydes and ketones, it follows that there should be bond enthalpy parameters that involve the carbonyl carbon that are also different for aldehydes and ketones. Therefore, there are C′—H (type 157-5), C—C′ (type 1-157), and C′=O (type 157-7) bond enthalpy parameters for the aldehydes and C—C′ (type 1-3) and C′=O (type 3-7) bond enthalpy parameters for the ketones. By the same logic, five-membered ring compounds have their own C—C′ (type 123-3) bond enthalpy parameter. There are no separate structural enthalpy parameters (ME′, SEC′, etc.) for aldehydes and ketones because this option would have greatly increased the number of enthalpy parameters to be optimized and was found to be unnecessary.

The POP term,[2] which includes the enthalpy contribution from the population of different conformers of a molecule, is accounted for in the heat of formation calculation. For the open-chain compounds, the number of possible conformers increases exponentially with the increasing length of the hydrocarbon side chain. Therefore, the POP term becomes larger and contributes significantly to the calculated heat of formation. For those mole-

TABLE I.
Number of Bond and Structural Enthalpy Parameters for Carbonyl Compounds.

Compound	C′=O Type 157-7	C′—C Type 157-1	C′—H Type 157-5	C′=O Type 3-7	C′—C Type 3-1	C′—C Type 3-123	ME′	SEC′	TERT′	NEO′	ISO′	TOR
Acetaldehyde	1	1	1	0	0	0	1	0	0	0	0	0
Propanal	1	1	1	0	0	0	0	0	0	0	0	1
Butanal	1	1	1	0	0	0	0	0	0	0	0	2
Pentanal	1	1	1	0	0	0	0	0	0	0	0	3
Hexanal	1	1	1	0	0	0	0	0	0	0	0	4
2-Methylpropanal	1	1	1	0	0	0	0	1	0	0	0	1
2-Ethylhexanal	1	1	1	0	0	0	0	1	0	0	0	5
2,2-Dimethylpropanal	1	1	1	0	0	0	0	0	1	0	0	1
3,3-Dimethylbutanal	1	1	1	0	0	0	0	0	0	1	0	2
3-Methylbutanal	1	1	1	0	0	0	0	0	0	0	1	2
Acetone	0	0	0	1	2	0	2	0	0	0	0	0
2-Butanone	0	0	0	1	2	0	1	0	0	0	0	1
2-Pentanone	0	0	0	1	2	0	1	0	0	0	0	2
3-Pentanone	0	0	0	1	2	0	0	0	0	0	0	2
2-Hexanone	0	0	0	1	2	0	0	0	0	0	0	3
3-Hexanone	0	0	0	1	2	0	0	0	0	0	0	3
4-Heptanone	0	0	0	1	2	0	0	0	0	0	0	4
5-Nonanone	0	0	0	1	2	0	0	0	0	0	0	6
6-Undecanone	0	0	0	1	2	0	0	0	0	0	0	8
3-Methyl-2-butanone	0	0	0	1	2	0	1	1	0	0	0	1
3,3-Dimethyl-2-butanone	0	0	0	1	2	0	1	0	1	0	0	1
3-Methyl-2-pentanone	0	0	0	1	2	0	1	1	0	0	0	2
3,3-Dimethyl-2-pentanone	0	0	0	1	2	0	1	0	1	0	0	2
4-Methyl-2-pentanone	0	0	0	1	2	0	1	0	0	0	1	2
4,4-Dimethyl-2-pentanone	0	0	0	1	2	0	1	0	0	1	0	2
2-Methyl-3-pentanone	0	0	0	1	2	0	0	1	0	0	0	2
2,2-Dimethyl-3-pentanone	0	0	0	1	2	0	0	0	1	0	0	2
2,4-Dimethyl-3-pentanone	0	0	0	1	2	0	0	2	0	0	0	2
2,2,4-Trimethyl-3-pentanone	0	0	0	1	2	0	0	1	1	0	0	2
2,3,4-Trimethyl-2-pentanone	0	0	0	1	2	0	1	0	1	0	1	2
3,3,4,4-Tetramethyl-2-pentanone	0	0	0	1	2	0	1	0	1	1	0	2
2,6-Dimethyl-4-heptanone	0	0	0	1	2	0	0	0	0	0	2	4
Di-*tert*-butyl ketone	0	0	0	1	2	0	0	0	2	0	0	2
tert-Butyl noepentyl ketone	0	0	0	1	2	0	0	0	1	1	0	3
Dineopentyl ketone	0	0	0	1	2	0	0	0	0	2	0	4
Cyclopentanone	0	0	0	1	0	2	0	0	0	0	0	0
Cyclohexanone	0	0	0	1	2	0	0	0	0	0	0	0
Cycloheptanone	0	0	0	1	2	0	0	0	0	0	0	0
Cyclooctanone	0	0	0	1	2	0	0	0	0	0	0	0
Cyclononanone	0	0	0	1	2	0	0	0	0	0	0	0
Cyclodecanone	0	0	0	1	2	0	0	0	0	0	0	0
cis-2-Hydrindanone	0	0	0	1	0	2	0	0	0	0	2	0
trans-2-Hydrindanone	0	0	0	1	0	2	0	0	0	0	2	0
trans-8-Methyl-2-hydrindanone	0	0	0	1	0	2	0	0	0	1	1	0
cis-8-Methyl-2-hydrindanone	0	0	0	1	0	2	0	0	0	1	1	0
cis-Bicyclo[3.3.0]octan-2-one	0	0	0	1	0	2	0	1	0	0	1	0
trans-Bicyclo[3.3.0]octan-2-one	0	0	0	1	0	2	0	1	0	0	1	0
Norbornan-2-one	0	0	0	1	0	2	0	1	0	0	1	0
Norbornan-7-one	0	0	0	1	0	2	0	2	0	0	0	0

TABLE I.
(Continued)

Compound	C′=O Type 157-7	C′—C Type 157-1	C′—H Type 157-5	C′=O Type 3-7	C′—C Type 3-1	C′—C Type 3-123	ME′	SEC′	TERT′	NEO′	ISO′	TOR
Bicyclo[2.2.2]octan-2-one	0	0	0	1	2	0	0	1	0	0	1	0
Bicyclo[3.2.1]octan-2-one	0	0	0	1	1	1	0	1	0	0	0	0
Bicyclo[3.2.1]octan-3-one	0	0	0	1	2	0	0	0	0	0	2	0
Bicyclo[3.2.1]octan-8-one	0	0	0	1	0	2	0	2	0	0	0	0
Bicyclo[3.3.1]nonan-3-one	0	0	0	1	2	0	0	0	0	0	2	0
Bicyclo[3.3.1]nonan-9-one	0	0	0	1	2	0	0	2	0	0	0	0
Adamantanone	0	0	0	1	2	0	0	2	0	0	0	0
Diadamantanone	0	0	0	1	2	0	0	2	0	0	2	0
1-Methylnorcamphor	0	0	0	1	0	2	0	0	1	0	1	0
Camphor	0	0	0	1	0	2	0	0	1	1	1	0
Total times each parameter is used	10	10	10	49	73	25	13	23	12	9	23	85

cules larger than propanal and 2-butanone, stochastic searches were performed for each compound with increasing kick size (Å) with increasing length of the hydrocarbon side chain(s) of the molecule. The POP term for each molecule was then calculated based on the enthalpy (ΔH) and entropy (ΔS) values for each of those conformers found in the stochastic search.[31] This method is essentially the same as doing the POP calculation based on ΔG and degeneracy values described earlier, but the former method is less prone to error in data input because the degeneracy is already incorporated into the ΔS term. As a precaution, the energy cutoff for ignoring the higher energy conformers in the calculation was 3.0 kcal mol^{-1} above the lowest energy conformer. For the compounds 2-ethylhexanal and 6-undecanone, the conformers in the 2.5–3.0 kcal mol^{-1} range were very numerous and contributed significantly to their POP terms.

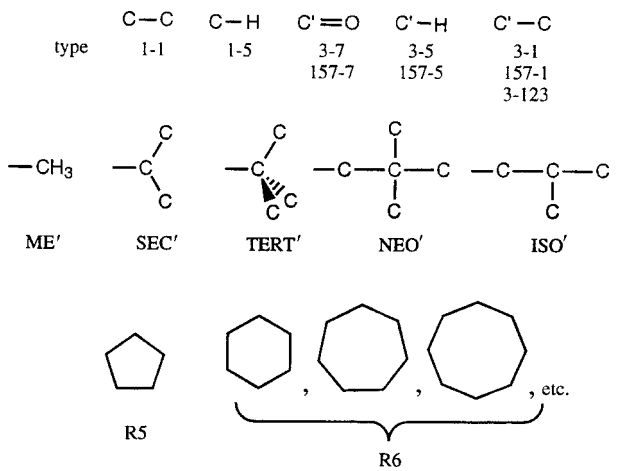

FIGURE 1. The bond and structural enthalpy parameters for carbonyl compounds.

Results

The optimized bond and structural enthalpy parameters for MM4 are listed in Table II. The structural enthalpy parameters for five- and six-membered rings (R5 and R6) and the TOR term were already fixed in the MM4 program and could not be optimized in the MM4 heat of formation calculations.

TABLE II.
MM4 Bond and Structural Enthalpy Parameters for Carbonyl Compounds.

Bond	Type	kcal mol^{-1}	Structure	kcal mol^{-1}
C′=O	3-7	−202.5000	ME′	0.2366
C′=O	157-7	−206.6800	SEC′	−2.0522
C′—C	3-1	−78.3254	TERT′	−4.2367
C′—C	157-1	−80.4100	NEO′	−1.1885
C′—C	3-123	−80.2354	ISO′	−0.3603
C′—H	157-5	−83.4029	TOR	0.5715 (fixed)
			R5	4.4694 (fixed)
			R6	4.9446 (fixed)

The TOR, R5, and R6 parameters were already set to fixed values in the MM4 program, so there were 11 adjustable parameters used for these compounds.

TABLE III.
Heats of Formation for Aldehydes and Ketones (kcal mol^{-1}).

Compound	Experiment		MM3[a]			MM4		
	ΔH_f	Ref.	Wgt.	ΔH_f	Dev.	Wgt.	ΔH_f	Dev.
Open chain								
Acetaldehyde	−39.73 (0.12)	10	10	−40.05	−0.32	10	−39.51	0.22
Propanal	−44.36 (0.21)	11	10	−44.75	−0.39	8	−44.51	−0.15
n-Butanal	−49.36 (0.37)	10	8	−49.72	−0.36	7	−49.73	−0.37
Pentanal	−54.61 (0.41)	11	5	−54.63	−0.02	4	−54.83	−0.22
Hexanal	−59.37 (0.38)	11	5	−59.54	−0.17	3	−59.87	−0.50
2-Methylpropanal	−51.58 (0.22)	11	8	−51.92	−0.34	8	−51.46	0.12
2-Ethylhexanal	−71.60 (0.48)	11	0	−69.72	1.88	3	−70.95	0.65
2,2-Dimethylpropanal	—	—	0	−59.18	—	0	−58.83	—
3,3-Dimethylbutanal	—	—	0	−64.77	—	0	−65.41	—
3-Methylbutanal	—	—	0	−56.98	—	0	−57.20	—
Acetone	−51.90 (0.12)	10	10	−51.91	−0.01	10	−51.86	0.04
2-Butanone	−57.02 (0.20)	10	10	−56.82	0.20	10	−56.95	0.07
2-Pentanone	−61.91 (0.25)	12	10	−61.78	0.13	7	−61.91	0.00
3-Pentanone	−61.65 (0.20)	12	9	−61.74	−0.09	9	−61.58	0.07
2-Hexanone	−66.87 (0.26)	12	9	−66.70	0.17	6	−66.89	−0.02
3-Hexanone	−66.50 (0.22)	12	9	−66.70	−0.20	6	−66.84	−0.34
4-Heptanone	−71.30 (0.31)	13	9	−71.66	−0.36	5	−71.86	−0.56
5-Nonanone	−82.44 (0.32)	12	6	−81.51	0.93	4	−82.29	0.15
6-Undecanone	−92.59 (0.47)	12	0	−91.35	1.24	1	−92.65	−0.06
3-Methyl-2-butanone	−62.75 (0.21)	12	10	−63.30	−0.55	8	−63.22	−0.47
3,3-Dimethyl-2-butanone	−69.47 (0.21)	12	10	−69.81	−0.34	8	−69.67	−0.20
3-Methyl-2-pentanone	−67.90 (0.32)	13	8	−67.21	0.69	7	−67.71	0.19
3,3-Dimethyl-2-pentanone	−72.60 (0.41)	13	6	−72.83	−0.23	7	−72.95	−0.35
4-Methyl-2-pentanone	−69.60 (0.34)	13	7	−68.92	0.68	7	−69.28	0.32
4,4-Dimethyl-2-pentanone	−76.60 (0.45)	13	8	−76.49	0.11	7	−76.44	0.16
2-Methyl-3-pentanone	−68.38 (0.21)	14	9	−68.24	0.14	7	−67.87	0.51
2,2-Dimethyl-3-pentanone	−75.00 (0.33)	14	7	−74.63	0.37	7	−74.66	0.34
2,4-Dimethyl-3-pentanone	−74.40 (0.26)	14	8	−74.47	−0.07	7	−74.58	−0.18
2,2,4-Trimethyl-3-pentanone	−80.85 (0.29)	14	—	—	—	8	−80.85	0.00
2,3,4-Trimethyl-2-pentanone	−78.50 (0.41)	13	6	−77.79	0.74	7	−78.34	0.16
3,3,4,4-Tetramethyl-2-pentanone	−83.10 (0.42)	13	5	−83.61	−0.51	7	−83.43	−0.33
2,6-Dimethyl-4-heptanone	−85.49 (0.29)	14	5	−85.48	0.01	5	−86.04	−0.55
Di-*tert*-butyl ketone	−82.65 (0.29)	14	8	−82.62	0.03	7	−82.33	0.32
tert-Butyl noepentyl ketone	−94.14 (0.55)	14	6	−94.18	−0.04	5	−94.53	−0.39
Dineopentyl ketone	−100.67 (0.84)	15	2	−100.63	0.04	2	−101.33	−0.66
Ring and fused ring								
Cyclopentanone	−46.03 (0.40)	10	8	−45.81	0.22	8	−46.24	−0.21
Cyclohexanone	−54.04 (0.52)	10	6	−54.44	−0.40	6	−53.43	0.61
Cycloheptanone	−59.3 (0.3)	16	0	−55.29	4.01	0	−55.90	3.40
Cyclooctanone	−65.1 (0.4)	16	0	−58.20	6.90	0	−58.02	7.08
Cyclononanone	−66.8 (0.4)	16	—	—	—	0	−61.88	4.92
Cyclodecanone	−72.9 (0.4)	16	—	—	—	0	−67.79	5.11
cis-2-Hydrindanone	−59.65 (0.31)	17	5	−59.91	−0.26	8	−59.56	0.09
trans-2-Hydrindanone	−59.56 (0.38)	17	5	−60.51	−0.95	8	−59.80	−0.24
cis-8-Methyl-2-hydrindanone	−65.77 (0.55)	18	3	−65.34	0.43	6	−65.19	0.58
trans-8-Methyl-2-hydrindanone	−68.59 (0.81)	18	2	−67.69	0.90	2	−67.92	0.67
cis-Bicyclo[3.3.0]octan-2-one	−55.0 (1.3)	19	—	—	—	0	−52.20	2.80
trans-Bicyclo[3.3.0]octan-2-one	−49.5 (1.3)	19	—	—	—	0	−43.32	6.13

TABLE III.
(Continued)

Compound	Experiment		MM3[a]			MM4		
	ΔH_f	Ref.	Wgt.	ΔH_f	Dev.	Wgt.	ΔH_f	Dev.
Norbornan-2-one	−40.1 (0.8)	20	0	−37.43	2.67	0	−37.89	2.21
Norbornan-7-one	−32.0 (0.7)	20	0	−28.47	3.53	0	−31.81	0.19
Bicyclo[2.2.2]octan-2-one	−52.1 (2.0)	21	0	—	—	0	−47.32	4.78
Bicyclo[3.2.1]octan-2-one	−52.1 (2.0)	21	0	−49.30	2.80	0	−50.29	1.81
Bicyclo[3.2.1]octan-3-one	−52.8 (2.0)	21	0	−51.52	1.28	0	−49.38	3.42
Bicyclo[3.2.1]octan-8-one	−46.1 (2.0)	21	0	−45.67	0.43	0	−44.55	1.55
Bicyclo[3.3.1]nonan-3-one	−60.7 (2.0)	21	0	−60.58	0.12	0	−58.74	1.96
Bicyclo[3.3.1]nonan-3-one	−57.4 (2.0)	21	0	−55.60	1.80	0	−52.54	4.86
Adamantanone	−55.1 (1.1)	22	0	−56.46	−1.36	0	−53.86	1.24
Diadamantanone	−56.5 (0.4)	23	0	−61.14	−4.62	0	−57.84	−1.34
1-Methylnorcamphor	−48.8 (0.6)	24	—	—	—	0	−45.52	3.28
Camphor	−63.9 (0.7)	25	0	−58.84	5.06	0	−57.66	6.24
Total rms deviation[b]				Standard 0.42 Weighted 0.39			Standard 0.35 Weighted 0.31	

[a] From ref. 8.

[b] Calculations for standard and weighted rms deviations were based on 35 weighted equations in MM3 and 38 weighted equations in MM4. The optimization and analysis ignored all equations whose weight was zero. The MM3 values for the calculated heats of formation and their weights were taken directly from the published MM3 work.[8] However, in this work, some of the experimental values were updated, and the MM3 rms deviations calculated here differ slightly from those in the MM3 article at 0.41 (for standard) and 0.40 (for weighted).

The calculated heats of formation are compared to the experimental values in Table III. In comparison to the MM4 results, the heats of formation were not calculated using MM3(94) in this work. The calculations are very laborious, especially for this number of compounds. Instead, the heats of formation calculated by Allinger et al.[8] using the older MM3(90) version of the program are listed. However, MM3(94) calculations on several small carbonyl compounds showed that the heats of formation calculated by the MM3(94) version of the program differed by no more than about 0.20 kcal mol^{-1} from the MM3(90) calculated values.

Although there are enough experimental data on the heats of formation for hydrocarbons to greatly overdetermine the system, there are only marginally enough accurate data for the carbonyl compounds.[10–25] Therefore, in the root mean square (rms) error calculation, the errors from the experiment were weighted according to the same scheme prescribed by Allinger et al.[8]: if the reported error in the experimental heats of formation was 0.2 kcal mol^{-1} or less, then the weight was 10; if it was in the range of 0.21–0.40 kcal mol^{-1}, the weight was 8; and for each 0.20 kcal mol^{-1} increment in error beyond this range, 2 more was subtracted from this weight. Thus, when the reported error was greater than 1.0 kcal mol^{-1}, then the weight was 0. The values of the POP and TOR terms, which are not accurately known quantities, also affected the weighting scheme. If POP + TOR $\geq$ 1.0, then 1 was also subtracted from this weight; when this sum was $\geq$2.0, then 2 was subtracted from this weight, and so on. As an example, for *n*-butanal the experimental ΔH_f° value[10] is -49.36 ± 0.37 kcal mol^{-1}. The calculated POP value was 0.53, the TOR value was $2 \times 0.57 = 1.14$, and POP + TOR = 1.67. The assigned weight for this molecule was therefore $10 - 2 - 1 = 7$.

In the MM3 study there were some molecules that were weighted zero, regardless of the above scheme, because we believed the experimental values were inaccurate. These same molecules were also weighted zero in the MM4 study. They were cycloheptanone thru cyclodecanone and the bridged bicyclic compounds (Table III). The experimental heats of formation for these compounds were far away from both the MM3 and MM4 calculated values. For the hydrocarbon analogs of these molecules, the calculated heats of formation almost ex-

actly agreed with the experimental values. We therefore strongly suspected that the experimental values for this group were in error. It is very difficult to obtain the ketone forms of some of these compounds in pure form. Most of them are waxy and form solid solutions, so their experimental heats of formation are unreliable in our opinion.

For most of the aldehydes and ketones listed in Table III, the MM3 and MM4 calculated heats of formation were both in good agreement with the experimental values. For the MM3(90) values the standard and weighted rms deviations were 0.42 and 0.39 kcal mol^{-1}, respectively, over a total of 35 weighted compounds. With MM4 there was significant inprovement from the MM3 calculated values. For the MM4 values the standard and weighted rms deviations were 0.35 and 0.31 kcal mol^{-1}, respectively, over the same set of compounds.

Conclusions

The necessary parameters for a heat of formation calculation for aldehydes and ketones was developed for MM4 using previously established methods.[2–7] Because the MM4 force field is in every way more accurate than the MM3 force field, we expected that it would give better heats of formation as well, unless the MM3 numbers were already limited by the accuracy of the data employed. The heats of formation calculated with MM4 were somewhat better than those calculated with MM3.

We excluded several compounds from our parameterization calculations for MM4, as we did for MM3, because we believed the experimental heats of formation to be in error. We repeatedly showed that the heats of formation can be accurately calculated for a wide variety of compounds and, when one stays within a well-studied class, significant discrepancies between the MM3 value and experiment were often the fault of the experiment, when the combustion was repeated (e.g., diisopropyl amine, isopropyl *t*-butyl ether, etc.).[27, 28] In some cases, the situation was less clear.[29] However, for the carbonyl compounds discussed here, we feel that a few are in error and a few may or may not be, because they are members of classes where the data are insufficiently well understood. An especially powerful method for checking the details of the errors is to also calculate the heat of formation by *ab initio* methods.[29, 30] When two of the three methods (*ab initio*, molecular mechanics, experiment) are in agreement and the third method is noticeably divergent, the third method is highly likely to be in error. Unfortunately, in a few cases the three numbers simply did not agree with each other at all, and in those cases the situation remains unclear.[29]

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