very friendly, pleasant, and professional. We also thank I. Mihutz and I. V. Gheorghiu for help in keeping the instrument running. We are very much indebted to Orhan Onur for his help in keeping us informed of some organic chemistry highlights and to Professors M. Christl (Würzburg) and H. Kessler (Frankfurt am Main) for making available their own work on related topics. We are indebted to Professor A. T. Balaban for helpful comments concerning our work.

Registry No. **4A**, 15577-76-1; **4B**, 109979-13-7; **4C**, 109979-14-8; **4D**, 109979-11-5; **5A**, 69501-60-6; **5B**, 110043-48-6; **5C**, 110043-49-7; **5D**, 109979-12-6; **6A**, 69501-61-7; **6B**, 84122-27-0; **6C**, 84122-28-1; **6D**, 109979-12-6; **7**, 27297-14-9; **8**, 31641-96-0; **9**, 27297-13-8; **10**, 31641-95-9; **13**, 4486-29-7; **15**, 1489-69-6; **18**, 4453-90-1.

New Molecular Mechanics (MM2) Parameters for Ketones and Aldehydes

J. Phillip Bowen*

Division of Medicinal Chemistry and Natural Products, School of Pharmacy, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27514

Ahammadunny Pathiaseril, S. Profeta, Jr., and Norman L. Allinger*

Department of Chemistry, School of Chemical Sciences, The University of Georgia, Athens, Georgia 30602

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The parameter set in MM2 has been changed to permit more accurate calculations on carbonyl compounds, taking into account ab initio calculations reported recently by Wiberg on 2-butanone and other data which have become available since the original formulation. Several major problems regarding carbonyl compound conformations and energies have been addressed, and the results are uniformly better than they were with MM2(77).

Ketones and aldehydes are important and widespread functional groups found in nature.[1] Numerous synthetic, conformational, and theoretical studies have focused on this broad class of carbonyl-containing compounds.[2] Carbonyl chemistry remains one of the fundamental methods for preparing complex chemical structures. Underlying the successful application of carbonyl chemistry has been an understanding of the geometric and conformational behavior of these compounds, which allows an investigator to make feasible predictions. Certainly, one of the chemist's major goals is to predict accurately the stereochemical course of reactions based on accumulated experimental and theoretical knowledge. Although transition-state geometries may differ significantly from ground-state geometries, a detailed knowledge of the latter is highly desirable.

The use of mechanical models for predicting conformational behavior has had laudable results, most notably with predictions on the stereochemical outcome of additions to the carbonyl moiety.[3] However, such models have relied, perhaps too heavily, on intuition, which may lead to errors.[4] More recently, powerful computational approaches to structure determination have been developed.[5,6] The molecular mechanics technique has been applied to a variety of functionalized molecules with generally excellent results. The molecular mechanics approach originally relied on empirically derived data and still does to a large extent. But it has long been known[7] that ab initio calculations can be used in place of experimental data. When the original MM2 ketone force field was first developed,[8] certain key conformational information was either sketchy or lacking altogether.[6,9] The purpose of this paper is to report a new set of MM2[10] parameters for ketones and aldehydes.[11]

Experimental and theoretical studies are constantly producing new insights into stereoelectronic and conformational behavior of molecules. Much of this new information is in agreement with MM2 predictions. In some cases, MM2 results have pointed out faulty experimental data, which has led experimentalists to reexamine their findings and correct the problems.[12] However, there are situations where new data have indicated errors in the force field,[13] which suggests that the initial data used to

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[1] Patai, S. *The Chemistry of the Carbonyl Group*; Interscience: New York, 1966.

[2] Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; American Chemical Society: Washington, DC, 1981.

[3] (a) Cram, D. J.; Wilson, D. R. *J. Am. Chem. Soc.* **1963**, *85*,k 1245 and earlier papers. (b) Karabatsos, G. J. *J. Am. Chem. Soc.* **1967**, *89*, 1367. (c) Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205. (d) Eliel, E. L.; Senda, Y. *Tetrahedron* **1970**, *26*, 2411. (e) Richer, J.-C. *J. Org. Chem.* **1965**, *30*, 324. (f) Marshall, J. A.; Carroll, R. D. *J. Org. Chem.* **1965**, *30*, 2748.

[4] (a) Wuts, P. G. M.; Walters, M. A. *J. Org. Chem.* **1984**, *49*, 4573. See ref 28. (b) Altona, C.; Farber, D. H. *Top. Curr. Chem.* **1974**, *45*, 1.

[5] The following reviews, books, and original literature citations therein are excellent sources of information: (a) Allinger, N. L. *Adv. Phys. Org. Chem.* **1976**, *13*, 1. (b) Engler, E. M.; Andose, J. D.; Schleyer, P. v. R., *J. Am. Chem. Soc.* **1973**, *95*, 8005. (c) Clark, T. *A Handbook of Computational Chemistry*; Wiley: New York, 1985. (d) Hehre, J. W.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986. Also, see ref 6.

[6] Burkert, U.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washington DC, 1982.

[7] Allinger, N. L.; Hickey, M. J. *Tetrahedron* **1972**, *28*, 2157.

[8] S. Profeta and N. L. Allinger. This work has never been published in the usual sense, but the results of it form the basis of the MM2 parameter set included in the original program (MM2(77)).

[9] Allinger, N. L.; Tribble, M. T.; Miller, M. A. *Tetrahedron* **1972**, *28*, 1173.

[10] Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127 and subsequent papers.

[11] Our philosophy has been and continues to be that we do not want the MM2 calculations to become time dependent. Since new data are constantly becoming available, if we were to incorporate it, the force field would be under constant change. We prefer not to do this. The errors known, which are many, are mostly small. In some cases where they are not very small, they are systematic and well understood and can be allowed for in an ad hoc fashion. However, in a few cases, we have found actual mistakes, typographical errors, and what not, and we have corrected those. In the present case, we feel that the improved data now available for ketones are sufficiently reliable and different that a revision of the ketone calculations is warranted. Versions of MM2 released after this time (which will be MM2(87) and subsequent) will contain these revisions. Earlier versions may be updated by the user by reading in the parameters shown in Table I. The original program is described in ref 10. The latest versions of the program are always available from the Quantum Chemistry Program Exchange, Department of Chemistry, University of Indiana, Bloomington, Indiana 47405, and from Molecular Design Limited, 2132 Farallon Drive, San Leandro, CA 94577. A list of current parameters is always available from N.L.A. (a reprint request card asking for current MM2 parameters is all that is needed).

[12] For example: Clark, T.; Knox, T. McO.; McKervey, M. A.; Mackle, H.; Rooney, J. J. *J. Am. Chem. Soc.* **1979**, *101*, 2404. Also, see ref 6.

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Table I. MM2(87), ab Initio, and Experimental Relative Energies

compounds	relative energies, kcal/mol MM2	exptl	ab initio
acetone			
eclipsed	0.00		
gauche	0.76	0.76	0.76
acetaldehyde			
eclipsed	0.00		
gauche	1.12	1.17	1.17
2-butanone			
eclipsed	0.00	0.00	0.00
gauche	1.44		1.37
skew	1.60	2.20	1.73
anti	2.37		3.12
1,4-cyclohexanedione			
chair	0.00		0.00
twist-boat	0.20	2.0 ± 0.7	0.00
cyclohexanone			
barrier	4.20	4.1 ± 0.1	
2-methylcyclohexanone			
equatorial	0.00		
axial	2.31	1.9 ± 0.3	
propionaldehyde			
eclipsed	0.00	0.00	0.00
gauche	2.15		2.20
skew	0.95	0.90 ± 0.1	1.27
anti	1.52	1.50 ± 0.1	1.75

Table II. Ab Initio Energies for 2-Butanone[a]

basis sets	dihedral angles	relative energies, kcal/mol	total energy, −hartrees
3-21G	0.0	0.00	229.70382
	60.0	2.20	299.70032
	120.0	2.46	229.69989
	180.0	4.26	229.69703
4-31G	0.0	0.00	230.65097
	60.0	1.46	230.64864
	120.0	1.73	230.64821
	180.0	3.10	230.64603
4-31G*	0.0	0.00	230.76779
	60.0	1.45	230.76548
	120.0	1.79	230.76494
	180.0	3.18	230.76271
6-31G	0.0	0.00	230.88916
	60.0	1.38	230.88696
	120.0	1.63	230.88657
	180.0	2.95	230.88446
6-31G*	0.0	0.00	230.99238
	60.0	1.37	230.99020
	120.0	1.73	230.98963
	180.0	3.12	230.98741

[a] Single-point GAUSSIAN 82 calculations were carried out on the MM2 minimized structures.

Table III. New Ketone and Aldehyde Molecular Mechanics Parameters

atom types				new torsional terms		
1	1	1	3	0.050	0.370	0.000
5	3	1	1	0.730	0.270	0.680
1	1	3	7	−0.130	0.904	0.050
1	1	3	1	1.200	0.200	0.150

parameterize MM2 were either incomplete or wrong. In general, it has been our view not to alter substantially the MM2 force field, in order to minimize the confusion and discrepancies among users of the different MM2 versions.[11] (These major changes have been reserved for a new generation of molecular mechanics programs called MM3, which will be the subject of future papers.) Nevertheless, there are situations where the new information is significant and compelling and where the corrections cannot be made in an ad hoc fashion, so that it seems desirable to reparameterize the force field in light of these new discoveries.

We have long been interested in ketone chemistry. For some time now there has been a growing body of evidence, in these laboratories and others, which suggests that the MM2 ketone force field, as originally parameterized, could not adequately reproduce some ab initio and recent experimental findings. During the original MM2 carbonyl parameterization process, ab initio calculations were carried out to augment sketchy or nonexistent experimental data.[7,8,14] Early quantum mechanical calculations at the 6-31G level[14] on MM2 geometries indicated that the energy curve around the skew conformation for 2-butanone was different from that of propionaldehyde.[15] The skew conformation has the methyl group rotated approximately 120° from the carbonyl oxygen. The global minimum has the methyl group eclipsed with the carbonyl oxygen and is well documented for a wide variety of carbonyl-containing compounds.[6,8] Complicating matters for the 2-butanone case, however, was a large range of experimental results with microwave, electron diffraction, and laser Raman which found the $\Delta E = 1.0\text{–}1.3$ kcal/mol in the liquid phase and 2.0–2.2 kcal/mol in the gas phase.[16] Therefore, a compromise among the data was reached, with 2-butanone being parameterized to have a minimum energy gauche conformation similar to propionaldehyde (see Table I and II).

Recently, Wiberg[17a] has reported a series of GAUSSIAN 82 caculations with full geometry optimization which indicate that the earlier GAUSSIAN 70 calculations were indeed correct; that is to say, the potential energy curve for 2-butanone is significantly flatter than the MM2(77) calculations predict. These results now present a consistent picture for the rotational potential as derived from double ζ basis set calculations, including those detailed by Schafer et al.,[17b] which included full geometry optimization at the 4-21G level. In addition, some elegant conformational studies by Goldsmith et al.[18] on 5,10-dimethyldecalin-

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(13) (a) Personal communication from Professor David J. Goldsmith. (b) Lipkowitz, K.; Allinger, N. L. *QCPE Bull.* **1987**, *7*, 19.

(14) (a) Unpublished work by N. L. Allinger and S. Profeta. GAUSSIAN 70 calculations gave a ΔE of 1.67 kcal higher for the skew than the eclipsed conformation of 2-butanone. (b) In 1981, 4-31G and 6-31G calculations were carried out by S. Profeta, Jr. (unpublished), to determine the torsional energy curve about the central bond in 2-butanone using MM2 geometries. No geometry optimization (gradient) was carried out, as the necessary program was not yet available to us. The curve obtained was essentially the same as that later published by Wiberg where full optimization was used. The earlier results were not published, because it was not certain at the time if they corresponded to reality, or if they were only an artifact of the use of MM2 geometries. The point is brought up here because we have long believed that using MM2 geometries and carrying out single point calculations would yield the same information as the much more expensive optimization within the ab initio method itself. Such has now been found to be true in the 2-butanone case. Finally, it is possible to correct the r_g values from a molecular mechanics calculation to r_e values which will be generated by an ab initio calculation by a simple adjustment of the l_0 values, with an additional correction for systematic errors resulting from small basis sets if desired. If one wants to geometry optimize in an ab initio calculation, this method should generally produce very accurate initial structures with a minimial amount of computing time.

(15) (a) Suter, V. W. *J. Am. Chem. Soc.* **1979**, *101*, 6481. (b) Rondan, N. G.; Paddon-Row, M. N.; Caramella, P.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2436. (c) Allinger, N. L.; Hickey, M. J. *J. Mol. Struct.* **1973**, *17*, 233. (d) Pickett, H. M.; Scroggin, D. G. *J. Chem. Phys.* **1965**, *61*, 3954.

(16) Shimanouchi, T.; Abe, Y.; Mikami, M. *Spectrochim. Acta, Part A* **1968**, *24A*, 1037. Abe, M.; Kuchitsu, K.; Shimanouchi, T. *J. Mol. Struct.* **1969**, *4*, 245.

(17) (a) Wiberg, K. B.; Martin, E. *J. Am. Chem. Soc.* **1985**, *107*, 5035. (b) Siam, K.; Van Alsenoy, C.; Klimkowski, V. J.; Ewbank, J. D.; Schaefer, L. *THEOCHEM* **1984**, *19*, 327.

(18) Goldsmith, D. J.; Bowen, J. P.; Qamhiyeh, E.; Still, W. C. *J. Org. Chem.* **1987**, *52*, 951.

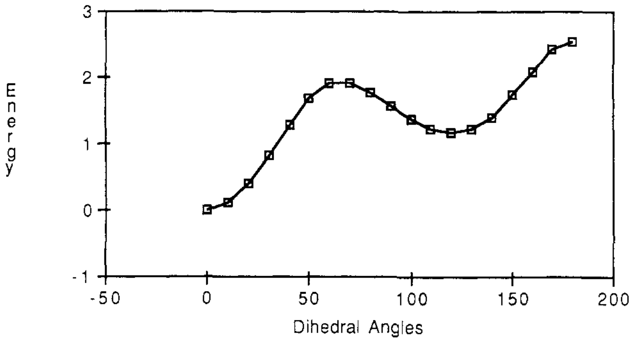

Figure 1. MM2 calculated energy curve for 2-butanone with the old carbonyl parameter set.

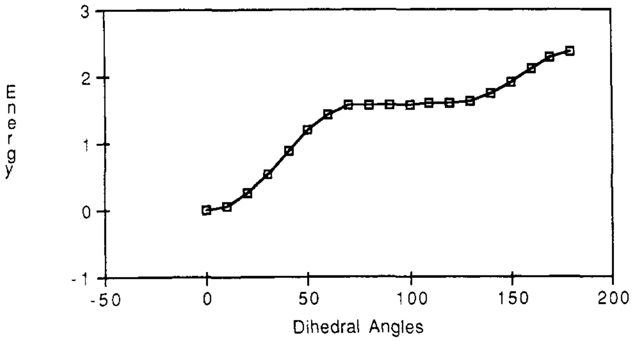

Figure 2. MM2 calculated energy curve for 2-butanone with the new carbonyl parameter set.

1,4-diones have indicated that MM2 calculations for these compounds give results that are at variance with experiment.[19] The problems with the cyclic ketones of this latter type can be traced to two fundamental and interrelated problems. First, with the current MM2 parameter set, the energy well for the second conformation (skew) of 2-butanone is too deep, as discussed above. Second, MM2 overestimates the stability of the chair conformer of cyclohexane-1,4-dione by about 1.4 kcal/mol. Moreover, MM2 as originally parameterized does not fit the cyclohexanone energy barrier very well,[20] which is now believed not to be higher than 4.1 ± 0.1 kcal/mol.[21] Armed with this new information and by carefully adjusting four torsional parameters as displayed in Table III, we were able to duplicate reasonably the 2-butanone energy curve, the twist-chair equilibrium for cyclohexane-1,4-dione, and the critical cyclohexanone energy barrier.

We too have carried out up to 6-31G* restricted Hartree–Fock calculations on 2-butanone, single points, using our MM2-calculated geometries.[22] The ab initio energies,[17,22] which are presented in Table II, essentially match the new MM2 energies, with one perhaps marginal exception. At a 180° dihedral angle between the carbonyl oxygen and adjacent methyl group, the anti conformation, there is a Me/Me eclipsed conformation. Using the modified carbonyl parameters, we find that the MM2 energy is lower than the quantum mechanical result by 0.75 kcal/mol. There is a consistently observed difference between ab initio calculations on the one hand and experimental data and molecular mechanics on the other hand for the CH_3–X–CH_2–CH_3 eclipsed conformations.[6] The prototype ab initio vs. experimental and MM2-calculated energy barriers occurs with the butane barrier when the Me/Me groups are eclipsed.[23] The latest ab initio[24] result has the barrier equal to 6.0 kcal/mol (after inclusion of electron correlation), while MM2 and experiment each give the barrier as only 4.5 kcal/mol.[6,23,24] Since we preferentially fit MM2 to experimental data, we have a lower anti 2-butanone barrier, which is consistent within the general MM2 framework (see Figures 1 and 2). Further work is needed to reconcile these systematic differences between experiment and quantum chemical calculations.

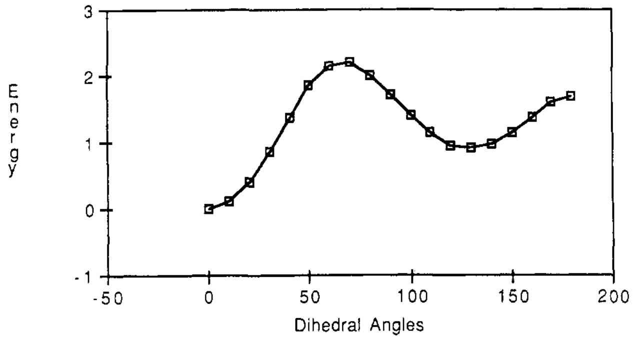

Figure 3. MM2 calculated energy curve for propionaldehyde with the new carbonyl parameter set.

Table IV. Ab Initio Energies for 1,4-Cyclohexanedione[a]

basis set	conformer	relative energy, kcal/mol	ab initio energy, -hartrees
3-21G	chair	0.00	379.45570
	twist	0.28	379.45526
4-31G	chair	0.31	381.02297
	twist	0.00	381.02346
4-31G*	chair	0.00	381.22139
	twist	0.04	381.22133
6-31G	chair	0.38	381.41711
	twist	0.00	381.41771
6-31G*	chair	0.00	381.59290
	twist	0.00	381.59290

[a] Single-point GAUSSIAN 82 calculations were carried out on the MM2 minimized structures.

Wiberg has more recently reported some calculations with methyl isopropyl ketone,[25,26] which we did not consider in the reparameterization process. The results with MM2(77) for this compound were not in good agreement with the GAUSSIAN calculations. The major discrepancy occurs at the conformation where the carbonyl group is midway between the methyl groups of the isopropyl; here, the MM2 energy is 1.8 kcal/mol higher than the ab initio value. With MM2(87), this value is reduced to under 0.4 kcal/mol.

Initially we had hoped to adjust the 1–1–3–1 (C_{sp^3}–C_{sp^3}–C_{sp^2}–C_{sp^3})[27] torsional potential by itself, without

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[19] W. C. Still has developed a modified ketone parameter set by fitting the force field energies to ab initio data obtained from Wiberg. See ref 17 and 18.

[20] The information on p 212 of *Molecular Mechanics* by Burkert and Allinger incorrectly reported that MM2 reproduced the cyclohexanone energy barrier (see ref 6). The acutal ring inversion barrier does not have the C–C(O)–C–C coplanar, as assumed in the early MM2 calculations. By using the Dihedral Driver Option and rotating about the C–C(O) bond of cyclohexanone, one obtains a barrier of 5.2 kcal/mol with the parameters incorporated in MM2(77). The new ketone parameters correctly fit this barrier.

[21] Anet, F. A. L.; Chmurny, G. N.; Krane, J. *J. Am. Chem. Soc.* **1973**, 95, 4423.

[22] Pople's GAUSSIAN 82 program was used for all of the reported ab initio calculations except where otherwise stated. GAUSSIAN 82 may be obtained from Professor Pople, Department of Chemistry, 4400 Fifth Avenue, Carnegie-Mellon University, Pittsburgh, Pennsylvania 15213.

[23] (a) Allinger, N. L.; Profeta, S., Jr. *J. Comput. Chem.* **1980**, *1*, 181. (b) Van-Catledge, F. A.; Allinger, N. L. *J. Am. Chem. Soc.* **1982**, *104*, 6272.

[24] Raghavachari, K. *J. Chem. Phys.* **1984**, *81*, 1383.

[25] Wiberg, K. B. *J. Am. Chem. Soc.* **1986**, *108*, 5817.

[26] We would like to thank Professor Wiberg for sending us his isopropyl methyl ketone ab initio calculations prior to publication.

Table V. Heat of Formation of Carbonyl Compounds[a,b]

Best Values

C=O = -24.525; C—C = -3.889; ME = -1.187; SEC = -1.285; TERT = -2.942

eq	wt	HF(O) calcd	HF(O) exptl	diff (calcd - exptl)	compound
1	10	-39.88	-39.73	-0.15	acetaldehyde
2	10	-44.76	-45.45	0.69	propanal
3	8	-49.77	-48.94	-0.83	butanal
4	5	-54.82	-54.45	-0.37	pentanal
5	5	-59.90	-59.37	-0.53	hexanal
6	8	-51.90	-52.25	0.35	2-methylpropanal
7	0	-70.33	-71.60	1.27	2-ethylhexanal
8	10	-51.99	-51.90	-0.09	acetone
9	10	-57.02	-57.02	0.00	2-butanone
10	10	-62.15	-61.92	-0.23	2-pentanone
11	9	-62.07	-61.65	-0.42	3-pentanone
12	9	-67.20	-66.70	-0.50	2-hexanone
13	9	-67.19	-66.51	-0.68	3-hexanone
14	9	-72.33	-71.30	-1.03	4-heptanone
15	6	-82.45	-82.03	-0.42	5-nonanone
16	0	-92.58	-92.55	-0.03	undecanone
17	10	-63.30	-62.76	-0.54	3-methyl-2-butanone
18	10	-69.49	-69.47	-0.02	3,3-dimethyl-2-butanone
19	7	-67.26	-67.90	0.64	3-methyl-2-pentanone
20	6	-72.04	-72.60	0.56	3,3-dimethyl-2-pentanone
21	7	-68.90	-69.60	0.70	4-methyl-2-pentanone
22	8	-75.84	-76.60	0.76	4,4-dimethyl-2-pentanone
23	9	-68.28	-68.38	0.10	2-methyl-3-pentanone
24	7	-74.42	-74.99	0.57	2,2-dimethyl-3-pentanone
25	8	-74.46	-74.40	-0.06	2,4-dimethyl-3-pentanone
26	6	-78.06	-78.50	0.44	3,3,4-trimethyl-2-pentanone
27	5	-83.05	-83.10	0.05	3,3,4,4-tetramethyl-2-pentanone
28	5	-85.38	-85.49	0.11	2,6-dimethyl-4-heptanone
29	8	-83.47	-82.64	-0.83	di-*tert*-butyl ketone
30	6	-92.96	-94.15	1.19	*tert*-butyl neopentyl ketone
31	2	-99.26	-100.67	1.41	dineopentyl ketone
32	8	-46.13	-46.03	-0.10	cyclopentanone
33	6	-53.97	-54.04	0.07	cyclohexanone
34	0	-55.35	-59.10	3.75	cycloheptanone
35	0	-57.10	-64.90	7.80	cyclooctanone
36	7	-58.66	-59.30	0.64	*cis*-hydrindan-2-one
37	7	-59.50	-59.70	0.20	*trans*-hydrindan-2-one
38	5	-63.57	-65.74	2.17	*trans*-8-methylhydrindan-2-one
39	4	-65.91	-68.56	2.65	*cis*-8-methylhydrindan-2-one

[a] The standard deviation = 0.8078. Based on 35 equations. Optimization and analysis ignore all equations whose weight is zero. [b] See ref 37.

adversely affecting other ketones. By making the V1 term positive, we were in effect increasing the energy minimum for the skew conformation of 2-butanone (at the desired 120° torsion angle about the C_{sp^3}–C_{sp^2} bond). This adjustment also reduced the energy gap between the twist and chair conformers of cyclohexane-1,4-diones. As is the case for so many "quick fixes", other important compounds were adversely affected.[28] In this case the energy difference between the axial and equatorial conformation of 2-methylcyclohexanone became too large.[6,29,30] By altering the 1–1–3–7 (C_{sp^3}–C_{sp^3}–C_{sp^2}–O)[27] torsion parameter, the errors with 2-methylcyclohexanone were essentially removed, so that the calculation then agreed with experiment.[6,29,30,31] In turn, by adjusting the 1–1–3–7 torsional constants, we affected the aldehydes. Propionaldehyde was our major test compound. By adjusting the 1–1–3–5 (C_{sp^3}–C_{sp^3}–C_{sp^2}–H)[27] dihedral parameters, we were able to offset the undesirable effects of the earlier 1–1–3–7 adjustments of this compound (see Table I and Figure 3).

Next, with these parameter changes made, we examined the critical cyclohexanone barrier and found that the energy had dropped from 5.2 to 4.3 kcal/mol, which is just on the high side of the experimentally determined NMR value. With only minor corrections to the 1–1–1–3 (C_{sp^3}–C_{sp^3}–C_{sp^3}–C_{sp^2}) torsion parameters, we were able to reduce the energy value to 4.2 kcal/mol, which is within experimental error of the reported 4.1 ± 0.1 kcal/mol barrier measured by Anet.[21]

Acetone is the simplest ketone, and the rotational barrier is well-known to be 0.76 kcal/mol.[32] Quantum mechanical

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[27] The MM2 program assigns specific atom types to each atom and hybridized state. For example, 1 = C_{sp^3}, 3 = C_{sp^2}(carbonyl), 7 = carbonyl oxygen, and 5 = alkyl hydrogen. A more complete listing of the atom types may be found in the MM2 manual.

[28] Jaime, C.; Osawa, E. *Tetrahedron* **1983**, *39*, 2769.

[29] (a) Allinger, N. L.; Blatter, H. M. *J. Am. Chem. Soc.* **1961**, *83*, 994. (b) Rickborn, B. *J. Am. Chem. Soc.* **1962**, *84*, 2414. (c) Cotterill, W. D.; Robinson, M. J. T. *Tetrahedron* **1964**, *20*, 765.

[30] The experimental ΔH results in ref 29 are 1.56, 1.95, and 2.16 kcal/mol, respectively. Therefore, the equilibrium value for the ΔH is an average value taken to be 1.9 ± 0.3 kcal/mol. In order to see if the axial and equatorial epimers solvate differently and somehow bias the results to favor the axial isomer, we carried out a series of solvation calculations using the IDME program (Dosen-Micovic, L.; Jeremic, D.; Allinger, N. L. *J. Am. Chem. Soc.* **1983**, *105*, 1723). A refined electrostatic picture was calculated with IDME and surrounded with various solvents. The energy of solvation was essentially identical for both axial and equatorial 2-methylcyclohexanone.

[31] We would like to thank Professor W. Clark Still and Glen Spears for sending us a summary of some equilibration studies for a number of cyclic ketones, including their results for 2-methylcyclohexanone.

[32] (a) Whangbo, M.-H.; Wolfe, S. *Can. J. Chem.* **1977**, *55*, 2778. (b) Cremer, D.; Binkley, J. S.; Pople, J. A.; Hehre, W. J. *J. Am. Chem. Soc.* **1974**, *96*, 6900. (c) Allinger, N. L.; Hickey, M. J. *Tetrahedron* **1972**, *28*, 2157. (d) Swalen, J. D.; Costain, C. C. *J. Chem. Phys.* **1959**, *31*, 1562. (e) Nelson, R.; Pierce, L. *J. Mol. Spectrosc.* **1965**, *18*, 344.

calculations also agree with this result. Therefore, we do not have any justification for altering this barrier, even if it would help to better describe the rotational potential of other molecules. MM2(87), as before, exactly reproduces this barrier.

The conformational studies on cyclohexane-1,4-dione have a rather long and conflicting history.[33,34] The data can all be rationalized in terms of a flexible and rapidly pseudorotating conformation which has the energy minimum at the D_2 twist-boat.[6] With the old parameters, MM2 calculations have the chair conformer 1.5 kcal/mole more stable (ΔH) than the twist-boat. Experimental Raman and infrared spectroscopy in the liquid phase gave $\Delta H = 2.0 \pm 0.7$ kcal/mol, favoring the latter.[33,34] Typically, the ΔH obtained by measurement of the temperature dependence of band intensities assumes that each of the two observed bands is unique to each of the two conformations. This fact, however, could not be established with certainty in this case, so the 2.0 kcal/mol value is uncertain. Previous STO-3G calculations indicated that the twist-boat conformer is 1.4 kcal/mol *higher* in energy than the chair, while the more flexible split-valence 3-21G calculations decreased this energy gap to 0.3 kcal/mol.[33] We have now carried out additional ab initio calculations on the chair and twist-boat structures (see Table IV).[22] The stability of the twist form increases relative to the chair slowly and irregularly with basis set size. The highest level restricted Hartree–Fock calculations that we did, using the 6-31G* basis set, have the twist and chair structures just equal in energy.[35] A favorable entropy for the flexible form still appears to be the best explanation for the preference of the experimentally observed twist-boat conformer. The new MM2 ketone parameters favor the chair by 0.2 kcal/mol, which is clearly more reasonable.

After making all of the necessary changes described to fit our set of test compounds, we applied our new parameters to the compounds reported by Goldsmith et al.[18] and found remarkably good agreement of the MM2(87) calculations with experiment.[36]

For a small set of compounds, parameters can always be changed to better fit the data.[28] However, to test the true generality of a parameter set, a large number of diverse compounds must be examined. Inasmuch as heats of formation are accurately known for a number of ketones and aldehydes, we compared the results of our new parameter set for the heat calculations on 35 diverse carbonyl compounds as previously treated by MM2. The results are shown in Table V. Our new standard deviation in the heat of formation between MM2(87) and experiment was 0.80 kcal/mol compared to 1.00 kcal/mol for the old (MM2(77)) ketone force field. The strainless heat parameters were also adjusted.[37] The longstanding and perplexing problem with the MM2 heat of formation for cyclohexanone has been resolved.

Therefore, we recommend that users of MM2 substitute the new ketone and aldehyde parameters for the ones presently incorporated into the program (both the torsional parameters in Table III and the heat of formation parameters in Table V). This new set of four torsional parameters reproduces some well-known and firmly established barriers such as acetone and propionaldehyde, while fitting to the quantum mechanically determined conformational energies of 2-butanone. The twist-chair equilibrium of cyclohexane-1,4-dione is now in much better agreement with the ab initio and experimental results, and the agreement with experimental equilibration data for a number of substituted 1,4-diones has improved. Moreover, the energy barrier for cyclohexanone now accurately reproduces the NMR measurements. Finally, the reduction of the standard deviation in the calculated heats of formation of the carbonyl compounds from 1.00 to 0.80 kcal/mol and all of this with only four torsional parameter changes indicate the generality of these newly formulated carbonyl parameters. These significant improvements have been obtained without any ill effects elsewhere, to our knowledge.

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Registry No. 2-Butanone, 78-93-3; propionaldehyde, 123-38-6.

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[33] Allinger, N. L.; Collette, T. W.; Carreira, L. A.; Davis, H. D.; Balaji, V.; Jordan, K. *Int. J. Spectrosc.* **1983**, *2*, 366.

[34] Allinger, N. L.; Wertz, D. *Rev. Latinoam. Quim.* **1973**, *4*, 127.

[35] 4-31G* and 6-31G* calculations were carried out on a CRAY X-MP at the Pittsburgh Supercomputer Center with the latest GUASSIAN 82 program written by Pople and co-workers.

[36] When several conformations of a single compound have similar steric energies, a Boltzmann calculation should be carried out to determine the mole fraction of each conformer present in the equilibrium mixture. Each mole fraction may then be multiplied by the respective steric energy and summed to determine the average heat content, ΔH, present in the system. The entropy of mixing and symmetry may be calculated, multiplied by the temperature, and subtracted from ΔH to yield the free energy, ΔG. Solution-phase conditions may be simulated with molecular mechanics by appropriately adjusting the dielectric constant. Goldsmith et al. (see ref 18) report a 76:24 ratio of trans/cis for a decalin-1,4-dione. MM2 calculations using the above-mentioned Boltzmann averaging and a 4.81 dielectric constant to simulate the $CDCl_3$ equilibration conditions gave a 77:23 ratio of trans/cis, which is certainly fortuitously close.

[37] The best values for the strainless heat parameters are as follows: C=O = −23.920, C–C = −3.920, ME = −1.940, SEC = 0.180, TERT = 0.210.