

Hydrogen Bonding in MM2

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Hydrogen bonding is qualitatively accounted for in the early versions of the MM2 program, but not quantitatively. Experimentally, the hydrogen bonds are somewhat shorter and stronger than calculated by MM2. This has been corrected now in MM2(87), by reducing the van der Waals radius of the hydrogen involved in hydrogen bonding for that interaction only, and by increasing the van der Waals' attraction between the hydrogen and the various electronegative atoms to which it can hydrogen bond by about 1–3 kcal/mol, depending on the particular atoms involved. It is now possible to reproduce reasonably well *ab initio* calculations on simple amides and the methanol dimer, and experimental data on compounds in which a hydroxyl hydrogen is hydrogen bonded to an alcohol, an alkyl chloride, or to a carbon–carbon double bond.

INTRODUCTION

Hydrogen bonding is believed to be largely an electrostatic phenomenon.¹ A proton having a low electron density about it, by virtue of being attached to an electronegative atom, will in general form a hydrogen bond with any electronegative atom which has an unshared electron pair, or with certain other systems such as an alkene or an aromatic ring. The strength of such hydrogen bonds can be quite variable, up to several kcal/mol. Certainly much of the attraction here is due to the simple electrostatics of the positive hydrogen and the negative lone pair. It is not clear whether some additional interaction may be required in order to model this interaction accurately. Accordingly, when the MM2 program was developed,^{2,3} no special provision was made for hydrogen bonding. It was hoped that the dipole–dipole interactions in the program would automatically account for most or all of the hydrogen bonding. As it has turned out, much of the hydrogen bonding is, in fact, accounted for by the electrostatics in MM2, but there is an additional amount, generally from 1–3 kcal/mol, which is not accounted for by the dipole–dipole interaction using the numbers originally in the program. Additionally, the two electronegative atoms that share the hydrogen bond in general actually come closer together than in the MM2 representation, by several tenths of an ang-

strom. Earlier workers who have been interested in using more quantitative calculations involving hydrogen bonding in MM2 have devised methods for modifying MM2 to achieve this objective. One such method has been published (actually with MM1) by Taylor.⁴ Another treatment was published more recently (for MM2) by Kroon-Batenburg and Kanters.⁵ It was limited to a study of the water dimer, and the parameterization required an angular dependence. Other workers have concluded that angular terms are unnecessary.⁶ Vedani and Dunitz have also studied hydrogen bonding in crystals, and they do include an angular term.⁷ We have used an effective dielectric constant of 1.5 throughout, which is the standard MM2 (gas phase) value.

Hydrogen bonds may form between different kinds of electronegative atoms, and also between the various bonding states of these atoms, and the numerical values for the hydrogen bond energy vary considerably, depending on the atoms involved. We therefore thought it would be desirable to make a general study of this phenomenon, picking some typical examples, and quantitatively comparing previous MM2-calculated hydrogen bond energies and geometries with those obtained by either *ab initio* calculations or by experiment. If this could be done in a few typical cases, we felt that estimations could

then be made for other kinds of cases, and a full set of preliminary values for hydrogen bonds between various electronegative atoms could be established.

DISCUSSION

One decision to be made at the outset is the form of the additional function which is going to be used to supply the hydrogen bond energy. We know that the function has a minimum of energy (a negative number) at a definite distance (the length of the hydrogen bond), and that it must rise asymptotically to zero at infinite distance, and that there is a repulsion if one goes closer than the energy minimum. Whether this function has directional properties or not is unclear. Spectroscopic formulations of hydrogen bonding usually do have an angular dependence, but do not include electrostatics. However, since molecular mechanics calculations provide most of the hydrogen bonding energy through electrostatics, this may be true of most or all of the angular dependence as well. Accordingly, the simplest choice seemed to be to use an ordinary van der Waals function, which has the right general shape, and to assume that the hydrogen bond formation was isotropic with respect to this particular function. This, at least, would be a first approximation. If it proved to be less than fully satisfactory, it could be modified subsequently. We chose the ordinary van der Waals function already used in MM2, since this simplified the programming required. Then only the van der Waals' parameters appropriate for the different kinds of hydrogen bonds had to be determined.

If we consider ethanol as a specific typical example, how exactly will we deal with the hydrogen bonding? The hydrogen on oxygen already has special characteristics associated with it. It is referred to as type 21, as opposed to type 5 (hydrogen bonded to carbon). In general, all of the properties of the type 21 hydrogen (and other types of hydrogens) will continue to remain as they have been unless otherwise specified (Table I). At this point, we are primarily changing the van der Waals curve that involves the interaction of this hydrogen type 21 with any electronegative atom (chlorine, nitrogen, or carbon-carbon double bond, etc.). For each interaction of this latter

Table I. Revised parameters for hydrogen not involved in hydrogen bonding.

Atom type	EPS	R*
21	.036	0.95
23	.034	1.05
24	.015	0.90
28	.015	0.90

type, we will assign specific van der Waals-type parameters (ϵ and r) to that interaction. We will do this for all of the different kinds of hydrogens which we have in the force field. Thus we create Table II, where when any particular kind of acidic hydrogen is hydrogen

Table II. Hydrogen-bonding parameters as in MM2(87).

	Atom pair	ϵ_{AB}^a	Sum of R*
1	2.....21	1.10	2.340
*2	2.....23	0.40	2.340
*3	2.....24	1.00	2.340
*4	2.....28	1.00	2.340
5	6.....21	1.30	1.830
*6	6.....23	0.60	1.830
*7	6.....24	2.20	2.140
8	6.....28	2.40	2.140
9	7.....21	2.95	2.140
*10	7.....23	0.40	2.140
*11	7.....24	1.00	2.140
*12	7.....28	3.00	2.03
*13	8.....21	2.00	2.220
*14	8.....23	0.40	2.220
*15	8.....24	1.40	2.220
*16	8.....28	1.00	2.220
*17	11.....21	0.80	2.050
*18	11.....23	0.20	2.050
*19	11.....24	0.60	2.050
*20	11.....28	0.40	2.050
21	12.....21	3.60	2.430
*22	12.....23	0.20	2.430
*23	12.....24	0.60	2.430
*24	12.....28	0.40	2.430
*25	13.....21	0.80	2.580
*26	13.....23	0.20	2.580
*27	13.....24	0.60	2.580
*28	13.....28	0.40	2.580
*29	14.....21	0.60	2.720
*30	14.....23	0.40	2.720
*31	14.....24	0.40	2.720
*32	14.....28	0.20	2.720
*33	15.....21	0.40	2.510
*34	15.....23	0.20	2.510
*35	15.....24	0.40	2.510
*36	15.....28	0.20	2.510

^a $\epsilon_{AB} = (\epsilon_A \epsilon_B)^{1/2}$. Atom type 21 is a hydrogen bonded to an oxygen in an alcohol, 23 is the hydrogen of an amine, 24 is the hydrogen on a carboxyl group, and 28 is the hydrogen on an amide, vinyl alcohol, or the nitrogen of an ammonium salt. The other numbers have their usual MM2 significance. An * indicates an estimated value.

bonded to any particular kind of electronegative atom, there will be specific van der Waals parameters assigned to that particular interaction. In addition, for interactions which involve these hydrogens but do not involve hydrogen bonding (for example 1–21, 5–21, 15–21, 21–23) the ordinary (unbonded) parameters (Table I) are used in the usual way.

A few other changes have also been made. The sizes of the type 21 and 23 hydrogen atoms were too large compared to the type 28 hydrogen. The radii were accordingly reduced to 0.95 and 1.05 Å, respectively. These data are summarized in Table I.

After examining a few pieces of data concerning interactions of the above kind, we came to the conclusion that we could, as a first approximation, assign the hydrogen engaged in hydrogen bonding a radius of 0.4 Å for the hydrogen-bonded interaction, and the radius in Table I for any other kind of interaction. [The value was slightly modified subsequently in some cases for a better fit to known data (Table II).] Hence we then had only one atom-dependent variable to specify, the depth of the potential well describing the hydrogen bond formation between a particular kind of hydrogen and a particular kind of electronegative atom. There are many such interactions, only a few of which have been investigated. Generally speaking, the more acidic hydrogen is expected to form a stronger hydrogen bond. The more electronegative acceptor atom holds its electron pair more tightly, and therefore forms a weaker hydrogen bond, other things being equal. Some values were estimated for typical interactions, and followed through with explicit calculations, the results of which were compared with experiment. It was found that the initial estimates tended to be overly conservative, therefore all were multiplied by a suitable factor to bring them into reasonable agreement with the experimental values being checked. Thereby we arrived at the values given in Table II. Only a few of these have been explicitly worked out so far (as discussed below), the others are only estimates. (As usual in MM2, an asterisk in Table II means a preliminary, probably guessed, value.)

At a first glance through Table II, we see that the trends are as expected, and strong hydrogen bonds require up to about 3 kcal/

mol of energy from the hydrogen-bonding function. Weaker ones require less. Three kcal/mol is quite a lot of energy when one is looking at an equilibrium; clearly, one must take this effect into account in the cases of the stronger hydrogen bonds if one wants to obtain a reasonable representation of the energy. We believe the numbers arrived at in Table II are a much better approximation of reality than simply using electrostatics alone to account for hydrogen bonding, and we recommend that the next approximation for treating hydrogen bonding in MM2 is the one given here (and which is included in MM2(87), and later versions of the program). Note that one cannot simply read these numbers into older versions of the program, since the hydrogen-bonded hydrogen has these parameters only for the atom to which it is hydrogen bonded, and has ordinary parameters for all other interactions. (Probably the best approximation for use with older versions of the program would be to simply read in the ϵ numbers from Table II and 0.4 Å for the hydrogen radius. This would assure the correct hydrogen-bonded interactions; the other interactions of the hydrogen-bonding hydrogens are of lesser importance. Note, however, that this procedure is not recommended, but might be found useful in case of emergency. What is recommended is that interested parties secure a copy of MM2(87).)

The specific cases examined in developing Table II will now be discussed. The interaction of a water molecule with formamide was studied in some detail, with respect to different orientations of the interacting molecules. Good *ab initio* calculations are available for comparison.⁸ Additionally, 4-chloro-1-butanol⁹ and 4-pentene-1-ol¹⁰ were examined. These two molecules have been studied by electron diffraction, and they contain a quite stable conformation which is internally hydrogen bonded. Suitable choices were made of the values for ϵ in order to fit these data.

Water–Formamide

We have used the results of DZP self-consistent field (SCF) *ab initio* calculations⁸ to examine the interaction between water and formamide with different orientations, and to parameterize the two kinds of hydrogen bonds involved, 6–28 and 7–21. The re-

Table III. Hydrogen bond interaction energies.

Water-formamide complexes ^a	<i>Ab initio</i>	MM2(77)	New parameters ^b
I	-9.5	-4.54	-9.35
II	-6.7	9.09	-6.14
III	-6.0	1.63	-4.43
IV	-6.2	3.40	-4.34

^aSee ref. 8 for the four possible water-formamide complexes. Our Roman numerals correspond to the geometries in this paper.

^bNew epsilon and radius values; as in MM2(87).

sults are shown in Table III. Four possible hydrogen-bonded arrangements of this molecule pair were used.⁸ The final values for the parameters shown in Table II were found by fixing the *R* value at 2.14 [(1.74) + (0.40)] and varying the two epsilon values over a wide range to find the place where the root-mean-square (rms) value for the difference between the *ab initio* results and MM2 results at different distances was a minimum. It was checked and found that these parameters also gave minimum energy geometries that were very close to those found in the *ab initio* work.

Electron Diffraction Studies of 4-Chloro-1-butanol and 4-Pentene-1-ol

For both of these compounds, the *R* values were again determined by adding 0.40 to the *R* value for the electronegative atom. Then the epsilon value was varied until the percentage of hydrogen-bonded conformer in the Boltzmann distribution of conformations was approximately equal to that found experimentally. The results for 4-chloro-1-butanol are shown in Tables II and IV. Table IV also shows the results from Bastiansen et al.⁹ The last column contains the distribution of con-

formers resulting from our final parameter set. The final parameters for 4-chloro-1-butanol are shown in Table II. Final results for 4-pentene-1-ol showed that the hydrogen-bonded conformer made up 50.5% of the mixture, compared with 50% \pm 20% from the experiment.¹⁰

Methanol Dimer

This dimer has been very much studied theoretically. A rather thorough study was carried out by Jorgensen¹¹ using the STO-3G basis set and the Gaussian 74 program. The dimerization energies for 270 orientations of the dimer were calculated, and fit to a potential function. The STO-3G calculations were judged to be in adequate agreement with the best experimental and theoretical data.¹²⁻¹⁴ The dimerization energies and the oxygen-oxygen distances for both the linear and cyclic dimers were reported in this study.¹¹ The linear dimer was reported to be much more stable than the cyclic dimer. An *ab initio* study using a 6-31G* basis set has also been reported on the linear methanol dimer.¹⁵ This is the best theoretical study of the linear dimer that is known. According to this study the dimerization energy for the linear methanol dimer is -5.66 kcal/mol and the oxygen-oxygen distance is 2.95 Å. From consideration of his calculations, and the literature data,¹⁶ Jorgensen¹¹ concluded that the true value for the dimerization energy for the linear methanol dimer is approximately -5.50 kcal/mol, and the best value for the oxygen-oxygen distance is 2.79-2.89 Å. We have examined both the linear and cyclic methanol dimers. When we used our "standard parameters" from an earlier version of Table II, the cyclic dimer was found to be

Table IV. Distribution of conformers for 4-chloro-1-butanol Hedberg's models.

Conformer #	Model A	Model B	Model D	MM2(87)
1	2.5	0.6	9.6	14.1
2	8.3	8.8	11.3	14.4
3	15.5	20.8	10.7	10.6
4	20.4	21.0	8.4	9.4
5	8.2	3.7	6.6	6.1
6	6.0	1.7	4.8	4.7
7	0.0	10.1	3.0	4.3
8	0.0	0.0	2.9	3.1
10	13.7	4.8	2.4	5.1
11	25.4	28.5	40.3	24.7

more stable than the linear dimer, and we obtained an oxygen–oxygen distance in the linear dimer which was too large (2.964 Å), together with a reasonable dimerization energy (−5.57 kcal/mol). We therefore modified these hydrogen-bonding van der Waals' parameters for this particular pair, so that the linear dimer was calculated to be more stable than the cyclic dimer by about 0.2 kcal/mol and both the dimerization energy and the oxygen–oxygen distance in the linear dimer are in reasonable agreement with both Jorgensen's best values and the values reported in the 6-31G* study. It is these modified numbers which are included in Table II. The remainder of the values in Table II with an asterisk in the left margin are approximate values only, and subject to similar small changes when they are explicitly studied. The original estimated (approximate) values for the 6–21 interaction of Table II were $R^* = 2.14$ Å, $\epsilon = 1.80$, and the improved values were $R^* = 1.83$, and $\epsilon = 1.30$. The values calculated for the linear methanol dimer with the latest van der Waals' parameters (Table II) are 2.779 and −5.00, for the oxygen–oxygen distance and the hydrogen bond energy, respectively. A specific study of each of the interactions shown in Table II would probably lead to small adjustments of the numbers there, as in this example.

As a check, we also examined the heat of formation of ethylene glycol using the new hydrogen-bonding parameters. Whereas the original error in the calculated heat of formation was 0.79 kcal/mol too positive,¹⁷ the error with these new numbers is approximately 0.3 kcal/mol, too negative. The new result for the heat of formation seems to be in slightly better agreement with the experimental value.

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