Study of Hydrogen Bonding Interactions Relevant to Biomolecular Structure and Function

Ya-Jun Zheng and Kenneth M. Merz, Jr.*

Department of Chemistry, 152 Davey Laboratory, Pennsylvania State University, University Park, Pennsylvania 16801

Ab initio molecular orbital calculations were used to study hydrogen bonding interactions and interatomic distances of a number of hydrogen bonded complexes that are germane to biomolecular structure and function. The calculations were carried out at the STO-3G, 3-21G, 6-31G*, and MP2/6-31G* levels (geometries were fully optimized at each level). For anionic species, 6-31 + G* and MP2/6-31 + G* were also used. In some cases, more sophisticated calculations were also carried out. Whenever possible, the corresponding enthalpy, entropy, and free energy of complexation were calculated. The agreement with the limited quantity of experimental data is good. For comparison, we also carried out semiempirical molecular orbital calculations. In general, AM1 and PM3 give lower interaction enthalpies than the best *ab initio* results. With regard to structural results, AM1 tends to favor bifurcated structures for O—H-O and N—HO types of hydrogen bonds, but not for hydrogen bonds involving O-H—S and S-H—O, where the usual hydrogen bond patterns are observed. Overall, AM1 geometries are in general in poor agreement with *ab initio* structural results. On the other hand, PM3 gives geometries similar to the *ab initio* ones. Hence, from the structural point of view PM3 does show some improvement over AM1. Finally, insights into the formation of cyclic or open formate–water hydrogen bonded complexes are presented. © 1992 by John Wiley & Sons, Inc.

INTRODUCTION

The accurate representation of hydrogen bonding is important in the modeling of biological molecules because hydrogen bonding interactions have a role in determining the structure and activity of these systems. Therefore, extensive experimental and theoretical effort has been expended in an attempt to clearly understand this phenomenon.

Given the obvious importance of hydrogen bonding in molecules and condensed phases, it is not surprising that many current force fields for biological systems[1,2]† pay close attention to hydrogen bonded atom pairs. To obtain a reliable potential for hydrogen bonded pairs, a knowledge of the magnitude of these interactions and the interatomic distances is required. Although the distance information can be obtained from crystallographic data,[3] information concerning the interaction energy is not available in many cases. However, theoretical methods are able to and have provided this kind of information.

To enhance the next generation of molecular mechanical force fields for biomolecular simulation, a detailed understanding of hydrogen bonding patterns between polar groups in proteins and between polar groups in proteins and water is necessary. The former interactions control in part intramolecular interactions and dynamics, while the latter influences intermolecular interactions and dynamics of biomolecules. In an effort to attack this daunting problem, Clementi and coworkers, in 1972, reported a systematic investigation of the hydration of amino acids using *ab initio* techniques.[4] Due to the limitation of computer speed at that time, the geometries were only partially optimized and the calculations were done using a small basis set. Even by today's standards, systematically looking at the hydration of amino acids using sophisticated *ab initio* methods presents considerable difficulties. Hence, numerous recent authors have taken the approach to investigate small models that are indicative of the interactions present in biomolecules.[5–13]‡ This is a powerful approach and allows for the detailed understanding of individual cases, but it results in a fragmentation of the data and increases the difficulty in gathering trends, etc. present in the now quite extensive data base of hydrogen bonding information. To overcome this, we have undertaken an effort to look, in a systematic way, at many of the intra- and intermolecular interactions that are present within proteins and between proteins and their external environment.

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*Author to whom all correspondence should be addressed.

†For hydrogen bonding in the OPLS force field, see ref. 2a; for other force fields, see ref. 2c.

‡For experimental and earlier theoretical calculations, see ref. 10b.

Because we want to study these hydrogen bonded complexes at the highest level possible, model compounds were chosen in such a way as to best represent the system, while at the same time keeping the model simple. In higher pH solutions, polar groups such hydroxyl could possibly be ionized, so the deprotonated species are also included. The model compounds that were studied are presented in Scheme 1.

Another goal of this work is to systematically look at the performance of two recent semiempirical methods that are capable of realistically treating hydrogen bonding systems. For a fair comparison, it is necessary to convert all of the *ab initio* interaction energies into interaction enthalpies via corrections computed using vibrational frequencies. The reason for this is the fact that in a parametric method like AM1 or PM3 finite temperature effects and zero point energy (ZPE) are included. These effects are, of course, introduced in the parametrization scheme when experimental interaction enthalpies are used in this process. Hence, any critical assessment of the ability of a semiempirical method vs. an *ab initio* one requires thermodynamic and ZPE corrections. Previously, Rzepa et al.[14] * concluded that PM3 underestimates the hydrogen bond strength in the water dimer; however, they were comparing inter-

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*For other references on the hydrogen bonding characteristics of AM1, see ref. 14b.

CH₃OH   CH₃O   CH₃OCH₃   C₆H₅O⁻

   1   2   3   4

CH₃SH   CH₃S⁻   CH₃SCH₃

    5   6   7

HCO₂H   HCO₂⁻   CH₃NH₃⁺   CH₃NH₂

   8   9   10   11

12

13   14

a R=CH₃
b R=NH₂

15   16

Scheme 1

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action enthalpies (PM3) with interaction energies *(ab initio)*. This is clearly not a fair comparison and, in fact, after thermodynamic corrections 6-31G* and PM3 interaction enthalpies are similar (see below). Obviously, experimental information is crucial in all cases to assess the ability of any molecular model to accurately reproduce reality. It is hoped that from this comparison of the different methods that it will become clearer where semiempirical methods might excel and where they might fail. Given this information, better semiempirical methods can be produced in the future.
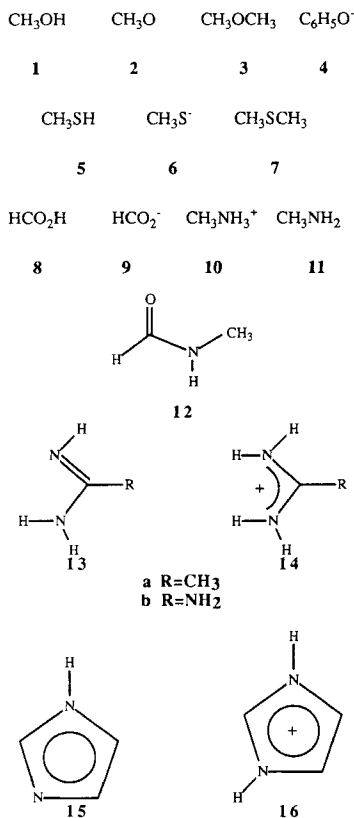
METHODS

Calculations were carried out using both *ab initio* and semiempirical molecular orbital methods. For the *ab initio* work, calculations were done using the Gaussian 88[15] and 90[16] programs, while the semiempirical research was carried out with AM1[17] and PM3[18] as implemented in the MOPAC and AMPAC2.1† programs. The AM1 sulfur parameters were those reported by Dewar and Yuan.[19] Geometries are fully optimized with respect to all geometric parameters. Symmetry is used only when it is necessary, and it will be pointed out whenever employed. In all cases, we have attempted to locate the global minimum on the potential energy surface. We have not explored most of the surfaces in detail with regard to how geometric variation affects the energetics of the potential energy surfaces.

No counterpoise corrections were made for the basis set superposition error (BSSE) because these corrections can only provide an approximate estimate on the error.[20,21] However, even for the water dimer there is still some debate regarding this issue.[22] Sometimes unrealistic results can occur after correction. For example, the alanine dimer gives an interaction energy of − 19.7 kcal/mol, while after the counterpoise correction it becomes + 14.4 kcal/mol.[23] Furthermore, it has been shown that 6-31G* gives fairly good interaction energies.[24,25] The low-level *ab initio* calculations were carried out only for comparison. The resulting geometries also served as an initial guess for the more elaborate calculations.

For all but the largest molecular complexes, we calculated vibrational frequencies at the 6-31G* level to compute the enthalpy, entropy, and free energy of complexation using standard procedures.[26] This was done to facilitate comparison with experimental quantities whenever possible, but it was also done to allow for a more accurate comparison with the semiempirical results. This is because the semiempirical methods directly evaluate the enthalpy of

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complexation and *ab initio* methods do not unless they are appropriately corrected. The entropies and free energies reported are for 298.15 K. The 6-31G* entropies and enthalpic corrections were used to obtain enthalpies and free energies using both 6-31G* and MP2/6-31G* energies. Finally, we note that the entropies are sensitive to the calculated vibrational frequencies (especially ones below ~500 cm^{-1}), so small free energy differences may not be quantitatively significant.

Given the lack of data for hydrogen bonding interactions between neutral monomers, it is difficult to identify at what level of sophistication we obtain the best agreement with experiment. The water dimer has been extensively studied both experimentally and theoretically and it has been found that the 6-31G* level of theory gives good agreement with what is thought to be the best experimental information,[20,25,27] but that correlated treatments at this level give interaction energies that are too negative.[20,25,27] However, once very large Hartree–Fock basis sets with correlation up to the MP4 level are employed agreement with experiment again improves.[26] Unfortunately, we cannot achieve this level of sophistication for all the systems we are studying. When it comes to hydrogen bonding interactions between charged and neutral molecules, there is much more experimental data and we and others[6] find that the correlated energies give the best agreement with experiment.

RESULTS AND DISCUSSION

We first calculated the total energy of the water molecule at different levels of approximation because this information is needed for several of the subsequent calculations. Obviously, numerous other authors have determined these values, but we recalculated them for convenience.[26] The calculated total energies for water are summarized in Table I.

Calculations for the hydrogen bonded complexes were carried out next and the total energies for all of the systems studied are also given in Table I. For convenience and clarity, the results for each hydrogen bonding system will be discussed individually in the following sections. In what follows, we will use the notation STO-3G, 3-21G, etc. to mean full geometry optimization instead of the STO-3G//STO-3G, 3-21G//3-21G, etc. formalism. We adopted this approach because we have carried out full geometry optimization in all cases and therefore the long-hand notation is redundant in our case. However, the long-hand notation will be used to describe previous workers' efforts in several cases.

Methanol–Water

This system has been studied previously at the STO-3G, 6-31G, and 6-31G* levels using fixed monomer

geometries,[5] but due to its importance in connection with hydrogen bonding interactions in proteins and carbohydrates it is desirable to get the interaction energy and interatomic distance as reliable as possible. Therefore, we decided to reinvestigate this system using full geometry optimization in conjunction with high-level *ab initio* methods.

Because both water and methanol can act as a donor or an acceptor, there are two hydrogen bonded complexes: one with water as acceptor (**17**) and the other with methanol as acceptor (**18**). Both complexes were investigated using semiempirical (AM1 and PM3) and *ab initio* methods. The calculated results are summarized in Tables II and III. Please note that in these and all remaining tables that the semiempirical results are given as interaction enthalpies and the *ab initio* data is given as interaction energies. Specific corrections of the latter information to generate interaction enthalpies will be discussed in the body of the text.

The STO-3G interaction energies are in good agreement with the larger basis set results, while 3-21G is probably too negative. The 6-31G*, 6-31G**, and 6-311G** methods all give interaction energies around 5-6 kcal/mol; however, inclusion of correlation at the MP2 level for the latter two basis sets increases the interaction energy by about 1.5–2 kcal/mol. These interaction energies are similar to those found for the water dimer[20,25,27] and the behavior of the *ab initio* calculations again parallels that observed for water.[20,25,27] Given previous experience with the water dimer it is likely that the MP2 values are too negative,[20,25,27] but given the lack of experimental data in this case it is not possible to be definitive in this regard. It is clear that 6-311G** (MP2/6-311G**), 6-31G** (MP2/6-31G**), and 6-31G* (MP2/6-31G*) give similar results. Thus, 6-31G* (MP2/6-31G*) should be sufficient for all subsequent calculations on neutral systems. All methods predict similar energies for both structures, which is in contrast with earlier fixed geometry calculation.[5c] The calculated structures at the MP2/6-31G* level are shown in Figure 1.

The calculated enthalpies, entropies, and free energies for **17** and **18** using the 6-31G*(MP2/6-31G*) interaction energies are −3.9 kcal/mol (−6.1 kcal/mol), −20.8 eu, and 2.3 kcal/mol (0.1 kcal/mol), and −3.8 kcal/mol (−5.8 kcal/mol), −20.3 eu, and 2.3 kcal/mol (0.3 kcal/mol), respectively. Hence, it appears that both these complexes are unstable on the free energy surface.

The *ab initio* and PM3 structures involve a single hydrogen bond between methanol and water; however, the AM1 structure (**19**) is trifurcated as was seen for the water dimer structure[28] (see Table III). The AM1 calculated interaction enthalpy (**19**, 5.2 kcal/mol) is in good agreement with the MP2/6-31G* values (**17**, −6.1 kcal/mol; **18**, −5.8 kcal/mol) but is in poorer agreement with the 6-31G* values (**17**,

Table Ia. Calculated total energies (au) and heats of formations (in kcal/mol, PM3 and AM1).[a]

Compound	STO-3G	3-21G	6-31G*	6-31+G*	MP2/6-31G*	MP2/6-31+G*	PM3	AM1
H_2O[b]	-74.9659012	-75.5859598	-76.0107465	-76.0177432	-76.1192442	-76.2122955	-53.43	-59.2
1[c]	-113.5491933	-114.3980192	-115.0354182		-115.3532946		-51.88	-57.0
2	-112.7063676	-113.7247971	-114.384719	-114.4111197	-114.7094977	-114.7520139	-37.94	-38.49
3	-152.138754	-153.2132080	-154.0647455		-154.5155452		-48.31	-53.20
4	-300.9891639	-303.2599233	-304.9689481				-44.11	-40.98
5	-432.8960776	-435.5262918	-437.7003192		-437.9678831		-5.53	-4.34
6	-432.1058878	-434.9588635	-437.1148635		-437.3810630	-437.4004179	-22.14	-16.98
7	-471.4827983	-474.3485836	-476.7353339				-10.96	-9.34
8	-186.2178841	-187.7001992	-188.7623096		-189.2518736		-94.41	-97.4
9	-185.4562769	-187.1046323	-188.1826260	-188.2081944	-188.6780570	-188.7220691	-110.91	-109.44
10	-94.4606317	-95.0593421	-95.5734912		-95.8761738		153.33	148.75
11	-94.0328628	-94.6816558	-95.2098286		-95.5144387		-5.19	-7.38
12	-205.2709552	-206.7991109	-207.9613496		-208.5707702		-42.48	-41.56
13[a]	-185.7431624	-187.0649479	-188.1186592		-188.7157227		7.61	8.25
13[b]			-204.1199417				13.29	18.69
14[a]	-186.2117206	-187.4806079	-188.5164321		-189.1028762		153.09	143.13
14[b]			-204.5215360				159.04	151.16
15	-221.9879949	-223.5491094	-224.8144294		-225.5411729		31.31	50.84
16	-222.4395568	-223.9457682	-225.1965516		-225.9144007		178.69	196.39
17[d]	-188.5252102	-190.0016497	-191.0550727		-191.5645934		-108.52	
18[e]	-188.5234850	-190.0019761	-191.0550190		-191.5649669		-108.23	-121.36 **(19)**
20	-187.7494423	-189.3712539	-190.461541	-190.4645267	-190.9570443	-191.0064084	-110.48	-114.02 **(21)**
22	-227.1073565	-228.8168003	-230.0839560		-230.7270173		-104.25	-116.94
24	-375.9895763	-378.8871574	-381.0074513				-110.79	-112.36 **(25)**
26	-507.8648540	-511.1208488	-513.7144490		-514.1728713		-59.80	-65.49
27	-507.8660772	-511.1228540	-513.7158834		-514.1748304		-61.39	-65.96
28	-546.4528554	-549.9475038	-552.7516452				-66.83	-71.02
29	-507.1173872	-510.5719104	-513.1484382		-513.6090421	-513.6399757	-87.59	-88.24 **(30)**
31	-261.2015556	-263.3194624	-264.7902727		-265.4741773		-153.61	-164.03 **(32)**
33	-260.4688404	-262.7383808	-264.2281768	-264.2550205	-264.9189506	-264.9678389	-180.66	-184.80
34	-260.4679280	-262.7303093	-264.2209058	-264.2504785	-264.9102067	-264.9623206	-178.47	-181.81 **(35)**
36	-169.4828580	-170.6935354	-171.6149914		-172.1110073		87.11	75.11 **(37)**
38	-169.0077871	-170.2841876	-171.2300329		-171.7281118		-61.24	-69.49
40	-280.2462099	-282.4022159	-283.9807998		-284.7817941		-97.67	-104.33 **(41)**
42	-280.2442017	-282.4040954	-283.9832393		-284.7845502		-99.73	-105.78 **(43)**
45	-371.9861724	-374.8117377	-376.9067331				-95.49	-92.56 **(46)**
47[f]	-371.9764898	-374.8142623	-376.8987227				-79.35	-75.87
48			-392.9083328				-88.42	-83.96
49			-292.9000249				-71.46	-66.48
50	-280.2675238	-282.4139255	-283.9903820		-284.7922283		-104.33	-107.53 **(51)**
52			-283.9566611[g]					
53	-296.9276170	-299.1539792	-300.8364321		-301.7541797		-25.49	-11.33 **(54)**
55	-296.9700694	-299.1551187	-300.3532010		-301.7558477		-25.35	-12.44 **(56)**
57	-280.2442017	-282.4040954	-283.9832393		-284.7845502		114.50	125.58 **(58)**

Table Ib. Calculated thermodynamic properties at the 6-31G* level.

Compound	E (kcal/mol)	S (eu)
H_2O	16.197	44.987
1	36.766	56.572
2	25.877	54.751
3	56.698	64.078
4	—	—
5	33.350	60.170
6	23.856	55.929
7	54.113	68.392
8	25.194	59.042
9	15.888	58.110
10	55.553	57.866
11	45.329	57.071
12	53.325	70.658
13[a]	61.379	68.621
13[b]	54.345	66.066
14[a]	70.446	70.465
14[b]	62.548	70.935
15	50.569	64.545
16	59.914	64.665
17	55.228	80.756
18	55.287	81.228
20	44.820	74.250
22	75.216	87.036
24	—	—
26	51.499	90.307
27	51.614	83.096
28	72.415	90.766
29	44.734	81.992
31	43.965	73.971
33	34.853	73.287
34	34.557	79.161
36	73.898	78.878
38	63.368	75.399
40	71.635	97.134
42	71.955	90.137
45	88.705	93.520
47	—	—
48	81.639	89.980
49	80.470	90.612
50	72.950	86.179
52	—	—
53	69.180	83.488
55	68.907	89.702
57	78.295	84.085

[a]For AM1, quite often the complexes have different geometries compared with PM3 and *ab initio* ones. In this case, the AM1 structures are indicated in parentheses.

[b]For water, we also did calculations at the 6-31+G, 6-31G**, 6-311G**, MP2/6-31+G, MP2/6-31G**, MP2/6-311G** levels. The calculated total energies are −75.9930588, −76.0236150, −76.0470120, −76.1284776, −76.2224487, and −76.2828957 au, respectively.

[c]For methanol, we also did full optimizations at the 6-31G**, 6-311G**, MP2/6-31G**, and MP2/6-311G** levels. The calculated total energies are −115.0467101, −115.075812, −115.3898435, and −115.4740685 au, respectively.

[d]This complex has also been fully optimized at the 6-31G**, MP2/6-31G**, and MP2/6-311G** levels, and the calculated total energies are −181.0791177, −191.6239302, and −191.7690805 au, respectively.

[e]For 18, we also did full optimizations at the 6-31G** and MP2/6-31G** levels, and the calculated total energies are −191.0789835 − 191.6243721, respectively.

[f]Symmetry was imposed because the zwitterionic species is not a minimum on the potential energy surface.

[g]Symmetry was used.

Table II. Calculated interaction energies for the methanol–water complexes.

Model	17 (kcal/mol)	18 (kcal/mol)
STO-3G	−6.28	−5.26
3-21G	−11.08	−11.30
6-31G*	−5.59	−5.55
6-31G**	−5.52	−5.43
6-311G**	−5.65	[a]
MP2/6-31G*	−7.80	−7.56
MP2/6-31G**	−7.30	−7.33
MP2/6-311G**	−7.70	[a]
PM3	−3.21	−2.92
AM1	−5.20	[b]

[a]Values were not determined.
[b]AM1 gives only one geometry in which the water interacts with methanol in a trifurcated manner.

−3.9 kcal/mol; **18**, −3.8 kcal/mol). PM3 gives structures similar to the *ab initio* methods (see Table III) and the interaction energies (**17**, −3.2 kcal/mol; **18**, −2.92 kcal/mol) are in good agreement with the 6-31G* values, but are much lower than the MP2/6-31G* values. The *ab initio* structures have the same overall shape, but the hydrogen bond distances do vary with STO-3G giving the shortest r(O—O) and r(O—H) distances and 6-31G* the longest, while inclusion of correlation tends to decrease the r(O—O) and r(O—H) distances to a value intermediate between the STO-3G and 6-31G* distances. PM3 geometries are more in line with the small basis set *ab initio* methods, but are close to the correlated geometries.

Methoxide–Water

The hydration of methoxide has been studied previously up to the MP2/6-31+G*//6-31G* level.[6] The calculated interaction energies and interatomic distances are shown in Table IV, together with the experimental hydration enthalpy value for comparison.[29] There are two sets of experimental data.[29,30] Early ion-cyclotron resonance (ICR) by Caldwell et al.[30] gave the hydration enthalpy of −19.9 kcal/mol for methoxide, but more recently Meot-Ner (Mautner)[29] examined the thermochemistry of hydrated clusters containing methanol and water and obtained an hydration enthalpy of −24 ± 1.0 kcal/mol for methoxide.[29]

The calculated enthalpy (using MP2/6-31+G* relative energies) and entropy differences are −24.3 kcal/mol and −25.5 eu for the reaction of methoxide with water to give **20**. The free energy of association is predicted to be −16.7 kcal/mol, which indicates **20** is stable on the free energy surface. The match between the calculated (−24.3 kcal/mol) and experimental enthalpy of hydration (−24 ± 1.0 kcal/mol) is excellent. The 6-31G* and MP2/6-31G* calculations both give too negative interaction energies, while the 6-31+G* and MP2/6-31+G* give inter-

Table III. Calculated interatomic distances for the methanol–water complexes.

Model	17		18	
	r(O—O) (Å)	r(O—H) (Å)	r(O—O) (Å)	r(O—H) (Å)
STO-3G	2.708	1.716	2.762	1.773
3-21G	2.772	1.800	2.712	1.808
6-31G*	2.961	2.014	2.952	2.008
MP2/6-31G*	2.898	1.930	2.867	1.929
MP2/6-31G**	2.893	1.933	2.856	1.934
PM3	2.760	1.812	2.775	1.819
AM1	2.457	2.260 (2.268)[a]		

[a]AM1 gives only one geometry in which the water interacts with methanol in a trifurcated manner.

action energies that are much less negative and for the latter in much better agreement with experiment when corrected. This is consistent with the notion that[26,31] the inclusion of diffuse functions is important for anionic systems. PM3 is in reasonable agree-

ment with the earlier experimental value, but is off by 4.9 kcal/mol with respect to the more recent value. AM1 matches relatively poorly with both values.

Again, the correlated calculations result in shorter r(O—O) and r(O—H) distances than those obtained at the restricted Hartree–Fock (RHF) level (see Table IV). The AM1 geometry is again bifurcated (**21**), which is at variance with our *ab initio* (**20**) and PM3 results, which both give a normal hydrogen bond geometry. The calculated MP2/6-31 + G* geometry is given in Figure 1, while selected bond distances are given in Table IV.

Dimethyl Ether–Water

The calculated interaction energies and the selected interatomic distances are given in Table V. Here, only one complex exists where water is the hydrogen bond donor. The STO-3G and 6-31G* calculations have been reported by previous researchers at fixed monomer geometries.[5]

The interaction energy results are similar to those obtained for the methanol–water case. STO-3G matches the 6-31G* calculation quite well, while 3-21G is too negative. Inclusion of correlation at the MP2 level again reduces the interaction energy by about 2 kcal/mol. Correction of the relative energies yields enthalpies of complexation of − 3.59 kcal/mol (6-31G* energies) and − 5.95 kcal/mol (MP2/6-31G* energies). The entropy is calculated to be − 22.03 eu, which in combination with the enthalpies of com-
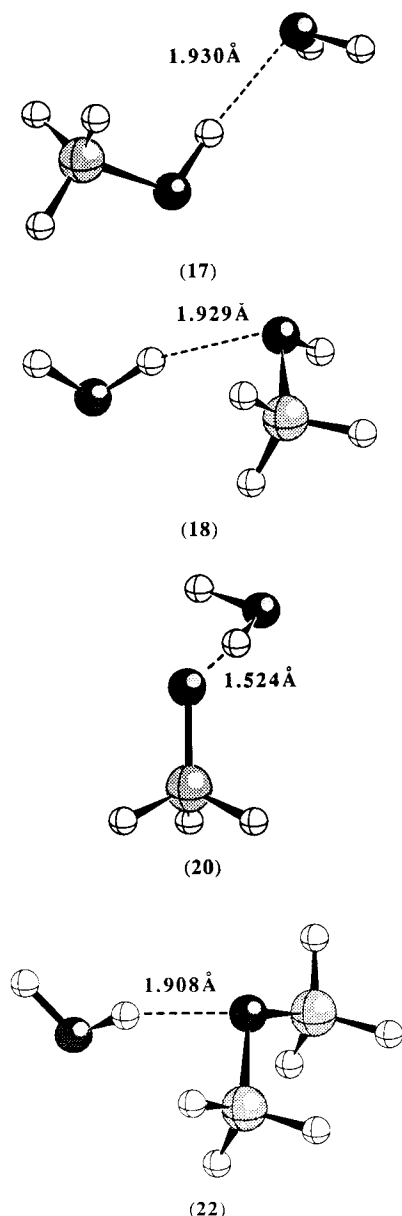

(17)

(18)

(20)

(22)

Figure 1. Calculated MP2/6-31G* (**17**, **18**, and **22**) and MP2/6-31 + G* (**20**) geometries.

Table IV. Calculated interaction energies and interatomic distances for the methoxide–water complex.

Model	Energy (kcal/mol)	r(O—O) (Å)	r(O—H) (Å)
STO-3G	− 48.40	2.367	1.263
3-21G	− 37.96	2.486	1.434
6-31G*	− 25.69	2.613	1.629
6-31 + G*	− 22.38	2.636	1.653
MP2/6-31G*	− 30.31	2.574	1.541
MP2/6-31 + G*	− 26.42	2.575	1.524
PM3	− 19.11	2.638	1.695
AM1	− 16.30	2.266	2.033 (2.100)
Expt.	− 24		

Table V. Calculated interaction energies and interatomic distances for the dimethylether–water complex.

Model	Energy (kcal/mol)	r(O—O) (Å)	r(O—H) (Å)
STO-3G	−4.76	2.782	1.794
3-21G	−11.06	2.722	1.814
6-31G*	−5.31	2.946	2.020
MP2/6-31G*	−7.67	2.880	1.908
PM3	−2.51	2.786	1.828
AM1	−4.50	2.652	2.234

plexation gives free energies of association of 2.98 and 0.62 kcal/mol, respectively. PM3 gives an enthalpy of association of −2.51 kcal/mol, which is in reasonable agreement with the 6-31G*-based enthalpy of interaction. AM1 is again more negative with respect to the latter value, but is in closer agreement with the MP2/6-31G* interaction enthalpy.

The STO-3G hydrogen bonding distances are again too small when compared to the bigger basis sets. Once again, AM1 favors the bifurcated structure (**23**). The *ab initio* and PM3 methods predict a normal hydrogen bonded complex with C_{2v} symmetry except the 3-21G geometry, which is slightly distorted away from C_{2v} symmetry. PM3 gives a geometry that is close to the MP2/6-31G* geometry but not the 6-31G* one. The STO-3G, 6-31G*, and MP2/6-31G* geometries are all pyramidal at the ether oxygen atom, which is similar to the water dimer.[31] The geometry is given in Figure 1 for MP2/6-31G*.

Phenolate–Water

Because phenol is more acidic than methanol, the hydrogen bonding interaction of phenolate with water is expected to be smaller than that of methoxide. The *ab initio* methods do indeed predict a smaller interaction energy for phenolate–water (see Table VI) and the same is also true for the semiempirical results. Due to the size of this system, calculations were stopped at the 6-31G* level, but it is clear that unlike methoxide (see Table IV) the bonding interaction of phenolate with water is less sensitive to the choice of basis set. The enthalpy and entropy was not determined in this case directly, but if we use the ~2 kcal/mol enthalpy correction observed for the methoxide–water case we predict that the enthalpy of interaction at the 6-31*G level would

Table VI. Calculated interaction energies and interatomic distances for the phenolate–water complex.

Model	Energy (kcal/mol)	r(O—O) (Å)	r(O—H) (Å)
STO-3G	−21.7	2.481	1.461
3-21G	−25.9	2.612	1.624
6-31G*	−17.4	2.750	1.796
PM3	−13.3	2.673	1.760
AM1	−12.2	2.593	2.103 (2.146)[a]

[a]The structure is bifurcated.

be about 15 kcal/mol. This places PM3 and AM1 in reasonable accord with the *ab initio* value.

The variation in bond distance is similar to that observed for the methoxide–water case (see Table IV), with the exception that the distances for the phenolate–water case are longer due to the weaker interaction. AM1 again gives a bifurcated structure while PM3 favors a normal hydrogen bond geometry, again is in good accord with the *ab initio* (6-31G* here) geometry. The 6-31G* (**24**) geometry is given in Figure 2.

CH₃SH–water

Because sulfur is a poor proton acceptor, the hydrogen bonding interaction is expected to be smaller than in the methanol–water case. Like the methanol–water system, there are two hydrogen bonded complexes. All methods predict a relatively small energy difference for these two complexes (see Table VII) and all methods predict that CH_3SH is a slightly better donor (resulting in **26**) than water. The difference between **26** and **27** is greater than that found in the methanol–water example (**17** vs. **18**). This is expected because the thiol hydrogen is more acidic than the methanol hydroxyl hydrogen.[33] The interaction energy trends are similar to the previous cases, but the magnitudes are about 60% of those observed for methanol–water.

For **26**, the calculated enthalpy, entropy, and free energy at the 6-31G*(MP2/6-31G*) level is −1.7 kcal/mol (−3.5 kcal/mol), −14.9 eu, and 2.7 kcal/mol (0.9 kcal/mol), while for **27** they are −0.7 kcal/mol (−2.1 kcal/mol), −22.1 eu, and 5.9 kcal/mol (4.5 kcal/mol), respectively. Interestingly, **26** has a less negative entropy contribution than does **27**, in contrast to the methanol–water case, where the entropy contributions were similar (**17** vs. **18**). This difference is probably due to the large difference in the hydrogen bonding distance between **26** and **27**, which is not seen in **17** and **18** (compare Figs. 1 and 3). PM3 is in good agreement with the 6-31G*-based enthalpies, while AM1 is in better agreement with the MP2/6-31G* values.

All methods predict the normal hydrogen bonding pattern and the geometries of **26** and **27** at the MP2/6-31G* level are given in Figure 3. The semiempirical and *ab initio* hydrogen bond distances are in reasonable accord with one another. AM1 does not give a bifurcated structure as it did for the methanol–water case; hence, it appears that the AM1 parameterization of sulfur is quite good.
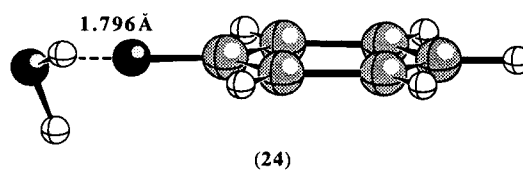

(24)

Figure 2. Calculated 6-31G* (**24**) geometry.

Table VII. Calculated interaction energies and interatomic distances for the thiol–water complex.

Model	26[a]			27[b]		
	Energy (kcal/mol)	r(O—S) (Å)	r(S—H) (Å)	Energy (kcal/mol)	r(O—S) (Å)	r(S—H) (Å)
STO-3G	−2.57	3.345	2.355	−2.45	3.435	2.103
3-21G	−6.65	3.468	2.767	−5.39	3.408	2.059
6-31G*	−3.02	3.591	2.803	−2.12	3.713	2.389
MP2/6-31G*	−4.83	3.462	2.640	−3.60	3.525	2.188
PM3	−2.43	3.439	2.480	−0.84	3.221	1.846
AM1	−2.50	3.370	2.457	−2.00	3.556	2.235

[a]Thiol as donor.
[b]Thiol as acceptor.

$(CH_3)_2S$–Water

For this system, there is one hydrogen bonded complex. In general, the bonding energies between $(CH_3)_2S$ and water are smaller than those for dimethyl ether–water. This is in agreement with the
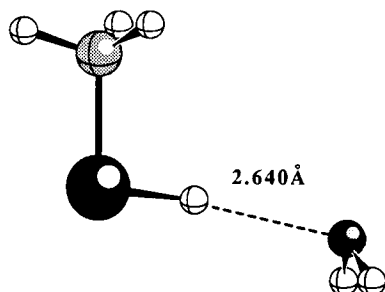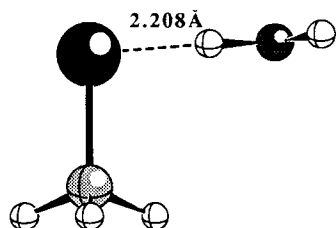

(26)
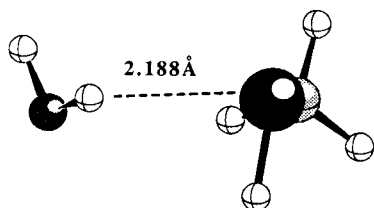
(27)
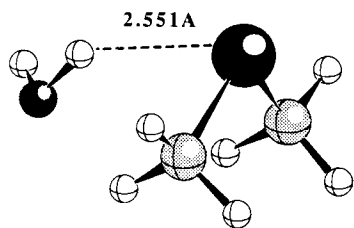
(28)

(29)

Figure 3. Calculated MP2/6-31G* (**26**, **27**, and **28**) and MP2/6-31 + G* (**29**) geometries.

electronegativities of oxygen and sulfur. All methods predict the sulfur center to be pyramidal and all methods except STO-3G predict a nonlinear hydrogen bond. The calculated results are shown in Table VIII. The interaction energy trends are similar to those observed for the previous cases.

Converting the relative energies into enthalpies of interaction yields −1.99 kcal/mol (6-31G*) and −4.39 kcal/mol (MP2/6-31G*). The entropy in this case is calculated to be −22.61 eu and this results in free energies of 4.75 and 2.35 kcal/mol, respectively. Again, this complex is not stable on the free energy surface. In this case, both AM1 and PM3 are in reasonable agreement with the 6-31G*-based enthalpy of interaction, while the MP2/6-31G* value is much more negative than either.

The nonlinear hydrogen bonding geometry of this complex seems to suggest that there are attractive interactions between the water oxygen and two of the six methyl hydrogens (see Fig. 3). Unlike the dimethyl ether–water situation, AM1 does not predict a bifurcated hydrogen bond; however, the angle between the C-S-C plane and the hydrogen bonding hydrogen is greater than the best *ab initio* values. The calculated PM3 geometry is again quite good.

CH_3S^-–Water

Because methyl thiol is more acidic than alcohol, the conjugate base (CH_3S^-) should be less basic than CH_3O^-. The theoretical calculations do predict the hydrogen bonding interactions to be weaker than in the case of methoxide (compare Tables IV and IX). Although there is no direct experimental data con-

Table VIII. Calculated interaction energies and interatomic distances for the thioether–water complex (**28**).

Model	Energy (kcal/mol)	r(O—S) (Å)	r(S—H) (Å)
STO-3G	−2.61	3.333	2.343
3-21G	−8.13	3.320	2.718
6-31G*	−3.49	3.491	2.726
MP2/6-31G*	−5.89	3.351	2.551
PM3	−2.44	3.454	2.496
AM1	−2.50	3.373	2.497

Table IX. Calculated interaction energies and interatomic distances for the thiolate–water complex (**29**).

Model	Energy (kcal/mol)	r(O—S) (Å)	r(S—H) (Å)
STO-3G	−28.61	2.868	1.829
3-21G	−16.98	3.275	2.398
6-31G*	−14.32	3.376	2.477
6-31+G*	−12.85	3.394	2.484
MP2/6-31G*	−18.03	3.201	2.246
MP2/6-31+G*	−17.11	3.189	2.208
PM3	−12.02	2.919	1.921
AM1	−12.06	3.091	2.501
Experimental	−14.2[a]		

[a]Experimental value for HS-(H₂O).

Table X. Calculated interaction energies and interatomic distances for the formic acid–water complex (**31**).

Model	Energy (kcal/mol)	r(O—O) (Å)	r(O—H) (Å)
STO-3G	−11.15	2.544	1.987
3-21G	−20.89	2.566	1.643
6-31G*	−10.80	2.796	1.882
MP2/6-31G*	−14.47	2.726	1.771
PM3	−5.77	2.676	1.780
AM1	−7.43	2.875	2.035

cerning the interaction enthalpy for this system, the interaction enthalpy between HS- and water is available (− 14.2 kcal/mol).[33] *Ab initio* calculations have also been reported for HS⁻(H₂O) and CH₃S⁻(H₂O)[6b,c] and it has been shown by Gao et al.[6b] that methylation has a very small effect on the hydration energy at the 6-31G* level. This was also true for single point calculations done at higher levels.[6b] Therefore, we might expect a similar interaction enthalpy for CH₃S⁻(H₂O) and HS⁻(H₂O). From our calculations, we arrive at interaction enthalpies of − 8.75 and − 13.0 kcal/mol for the 6-31 + G* and MP2/6-31 + G* levels, respectively. Assuming that the interaction enthalpy of − 14.2 kcal/mol is indicative of the thiolate–water case too, we see that the 6-31 + G* level is much too positive while the MP2/6-31 + G* values is in reasonable accord with experiment. AM1 and PM3 work quite well, but their interaction enthalpies are too positive by about 1 kcal/mol with respect to the best *ab initio* value and by 2 kcal/mol relative to the experimental value.

The geometries follow the usual trends and Figure 3 gives the geometry for the MP2/6-31 + G* (**29**). AM1 does not give a bifurcated structure, but the C-S—H angle is greater than that found for the MP2/6-31 + G* geometry. PM3 and STO-3G give too short hydrogen bonds in comparison with AM1 and the best *ab initio* structures.

Formic Acid–Water

Here, we only calculated the hydrogen bonded complex formed between the acidic carboxylic hydrogen and the oxygen atom of the water molecule. The results are shown in Table X. 4-31G* calculations have been reported previously for this complex.[7]

The calculated interaction enthalpies for this complex are − 8.26 and − 12.50 kcal/mol for interaction energies evaluated at the 6-31G* and MP2/6-31G* levels, respectively. The calculated entropy is − 30.06, which in combination with the previous interaction enthalpies yields free energies of interaction of 0.70 and − 3.5 kcal/mol. Hence, 6-31G* predicts that this complex is not stable on the free en-

ergy surface, while MP2/6-31G* predicts the opposite. The interaction enthalpies calculated using AM1 and PM3 are smaller than the best *ab initio* values, but are particularly too small when compared to the MP2/6-31G* value.

The resulting geometry for MP2/6-31G* (**31**) is given in Figure 4. The AM1 (**32**, not given) geometry is unusual because there are three hydrogen bonds in the AM1 structure while only two in the *ab initio* and PM3 structures. This is clearly due to the tendency of the AM1 treatment to favor the bifurcated structure. PM3, on the other hand, gives a geometry

(31)

(33)

(34)
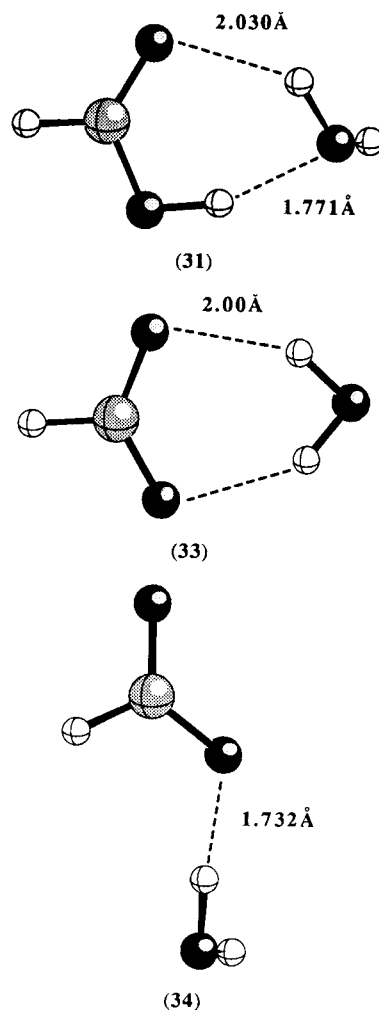
Figure 4. Calculated MP2/6-31G* (**31**) and MP2/6-31 + G* (**33** and **34**) geometry.

that is in good agreement with the best *ab initio* geometries (see Table X).

Formate–Water

The hydrogen bonded complex formed between formate and water has been examined by many researchers using optimized geometries given by smaller basis sets than those used here.[6b,8] The most stable complex adopts a C_2v structure wherein two hydrogen bonds are formed as in the carboxylic acid dimer. Due to the importance of this kind of interaction in biological chemistry, we decided to carry out further study on this system. The highest level used in our calculations is full geometry optimization at the MP2/6-31 + G* level, and the results are given in Tables XI and XII.

The interaction enthalpy between acetate ion and water has been measured by pulsed high-pressure mass spectrometry to be − 15.8 kcal/mol.[36a] Again assuming that methylation will have a minimal affect on the experimental interaction enthalpy[6b], we will use this value for our experimental formate-water interaction enthalpy. Meot-Ner has pointed out that the ring structure (**33**) is probably not favored under the experimental conditions. It was suggested that this interaction enthalpy might correspond to an open complex (**34**) since both water and methanol have similar interaction enthalpies for acetate.[35b] However, Gao et al.[6b] have shown that at the MP2/6-31 + G*//6-31G* level the ring structure is more stable than several possible open ones by ~3 kcal/mol. This difference has also been observed by Cybulski and Scheiner at the MP2/4-31 + G*//4-31 + G* level.[8f] The open structures studied by these authors were all planar and we have found that these structures move away from planarity once full geometry optimization is done. To obtain **34**, we started with the lowest energy planar minimum found by Gao et al.[6b] (their 10b) and Cybulski and Scheiner[8f] (their C-T), which has one water hydrogen hydrogen bonded *cis* to the C—H bond of formate while the remaining O—H bond is pointing away from the C—H bond of formate. Full geometric relaxation of the planar starting structure gives our **34**. Finally, the ring structure has not been observed in Monte Carlo simulations of formate and acetate ions in dilute solutions.[8e,36]

Table XI. Calculated interaction energies and interatomic distances for **33**.

Model	Energy (kcal/mol)	r(O—H) (Å)
STO-3G	− 29.28	1.429
3-21G	− 29.99	1.951
6-31G*	− 21.80	2.08
6-31 + G*	− 18.25	2.122
MP2/6-31G*	− 26.13	2.00
MP2/6-31 + G*	− 21.01	2.30
PM3	− 16.32	1.817
AM1	− 19.60	2.04

Table XII. Calculated interaction energies and interatomic distances for **34**.

Model	Energy (kcal/mol)	r(O—O) (Å)	r(O—H) (Å)
STO-3G	− 28.71	2.429	1.390
3-21G	− 24.92	2.623	1.637
6-31G*	− 17.28	2.750	1.801
6-31 + G*	− 15.40	2.761	1.816
MP2/6-31G*	− 20.65	2.725	1.732
MP2/6-31 + G*	− 17.54	2.742	1.754
PM3	− 14.13	2.657	1.730
AM1	− 16.60	2.568	2.069 (2.129)[a]

[a]The structure is bifurcated.

To build on previous efforts and test the possibility that **33** is not favored relative to **34**, we calculated the thermodynamic corrections. The calculated interaction enthalpies using the MP2/6-31 + G* interaction energies are − 18.8 and − 15.6 kcal/mol for **33** and **34**, respectively. The latter value of − 15.6 kcal/mol is in better agreement with the experimental interaction enthalpy. The calculated interaction entropies are − 29.8 and − 23.9 eu for **33** and **34**, respectively. This results in interaction free energies of − 9.92 and − 8.48 kcal/mol, which suggests that **33** is the lowest energy point even on the free energy surface. To study this interesting issue further, we also examined formate–methanol interactions, which were used by Meot-Ner to suggest that **34** is favored relative to **33**, because it is expected that the latter structure would be disfavored in the formate–methanol case due to the inability to form two hydrogen bonds in the ring structure. The calculations were carried out at the 6-31G* level only because this basis set gave similar results to the MP2/6-31 + G* calculations for **33** and **34** (see Tables XI and XII) and we expect this to be true for the formate–methanol case. The calculated results are summarized in Figure 5. The calculated interaction enthalpy for **33'** is close to that for the C_{2v} formate–water complex (**33**), as are the entropy and free energies. The calculated results for **34'** are similar to the open form of the formate–water complex (**34**). This results in the same conclusion that **33'** is favored on both enthalpy and free energy surfaces. It is also interesting to note that **33'** is similar to **33** and is also cyclic. Furthermore, the geometry of this complex seems to suggest that there is an O· · ·HC interaction. Similar interactions have been suggested by Meot-Ner[35] for other systems and have been observed such as in the crystal structure of acetic acid.[37]

Our results indicate that the ring complexes (**33** and **33'**) are more stable than the open ones (**34** and **34'**), in apparent disagreement with experimental conclusions. However, our interaction enthalpies for the open forms of these complexes are in excellent agreement with the experimental value of
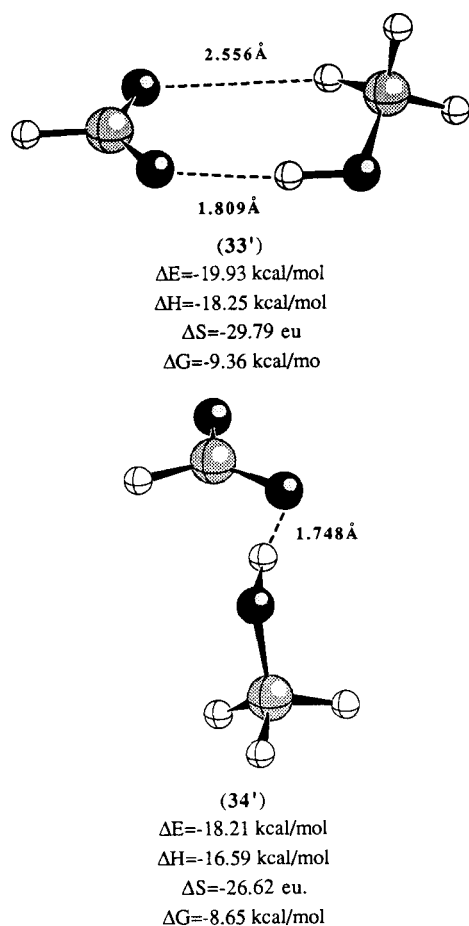
(33')

ΔE=-19.93 kcal/mol
ΔH=-18.25 kcal/mol
ΔS=-29.79 eu
ΔG=-9.36 kcal/mo

(34')

ΔE=-18.21 kcal/mol
ΔH=-16.59 kcal/mol
ΔS=-26.62 eu.
ΔG=-8.65 kcal/mol

Figure 5. Calculated geometries, interaction enthalpies, and interaction entropies for **33'** and **34'**.

Table XIII. Calculated interaction energies and interatomic distances for the methyl ammonium–water complex (**36**).

Model	Energy (kcal/mol)	r(O—N) (Å)	r(O—H) (Å)
STO-3G	−35.3	2.431	1.278
3-21G	−30.3	2.628	1.567
6-31G*	−19.3	2.813	1.791
MP2/6-31G*	−22.3	2.752	1.708
PM3	−12.8	2.754	1.778
AM1	−14.1	2.712	2.256 (2.259)[a]
Experimental	−18.4[b], −18.8[c]		

[a]The structure is bifurcated.
[b]See refs. 37a and 37b.
[c]See ref. 37c.

Methylammonium–Water

Table XIII shows the calculated interaction energies at several levels of approximations and the experimental data.[38] The interaction energy decreases as we increase the basis set size and inclusion of correlation at the MP2/6-31G* level decreases the 6-31G* value by about 3 kcal/mol. The previously reported interaction energy determined at the 6-31G*//3-21G level is about 2.5 kcal/mol smaller than our 6-31G*//6-31G* value. This difference is likely due to the restriction of the geometry in these calculations.[39] The calculated interaction enthalpies at the 6-31G* and MP2/6-31G* levels are −17.75 and −20.75 kcal/mol, respectively, with the former being in much better agreement with experiment than the latter. The calculated entropy is −23.98 eu compared to the experimental value of −21.8 eu[38] and the resulting interaction free energies are −10.6 and −13.6 kcal/mol, respectively. AM1 and PM3 give interaction enthalpies that are too low in all cases. This particular case represents the largest energetic difference between the semiempirical and ab initio methods up to this point. Because this is the first cationic-neutral and nitrogen-based system we looked at, the difference may be ascribed to the improper treatment of these variables by the semiempirical methods.[14]

Again, AM1 predicts a bifurcated structure (**37**), while both the ab initio and PM3 methods give similar structural results with the former displayed (**36**) in Figure 6.

Methylamine–Water

Water can be a hydrogen bond donor or acceptor in this case and we initially examined both. However, with water as a hydrogen bond acceptor we found that only the STO-3G and semiempirical methods gave a stable minimum for this complex. The larger ab initio basis sets predict that this complex is unstable and rearranges to the case where water is the hydrogen bond donor.
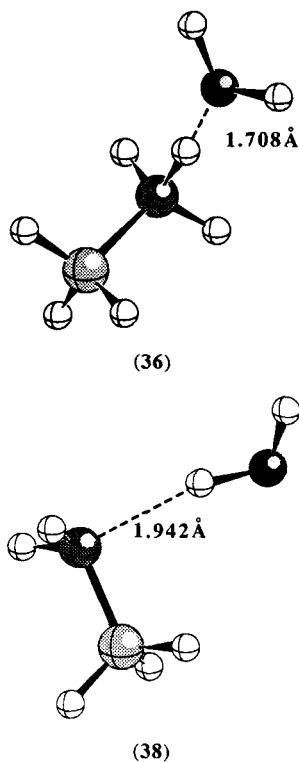
∼ −16 kcal/mol. Meot-Ner suggested that the ring complexes might not form due to the unfavorable entropy of the constrained structure. Our calculated entropies do indeed show this to be the case and we expect that Meot-Ner's interpretation is correct. However, vibrational frequencies obtained at the 6-31G* level still do not show an entropy differential large enough to favor **34** over **33** on the free energy surface.

Comparing the best ab initio interaction enthalpy (−18.8 kcal/mol) for the formation of **33** to that obtained by the semiempirical methods shows that PM3 is too low by about 2 kcal/mol and that AM1 is too negative by about 1 kcal/mol. Thus, it appears that the semiempirical methods perform quite reasonably here with regard to energetics.

While the geometries (see Fig. 4) for **33** calculated with all methods are similar, it is interesting to note that STO-3G predicts a structure with a near linear hydrogen bond, while the remaining methods predict a C_{2v} structure. For the open hydrogen bonded complex (**34**), AM1 again predicts a bifurcated structure, while PM3 gives a structure similar to the 6-31G* one.

(36)

(38)

Figure 6. Calculated MP2/6-31G* (**36** and **38**) geometries.

With water as a hydrogen bond donor we, not unexpectedly, find the interaction energy is much smaller than for the protonated species (Table XIV). In this case, the STO-3G value is reasonable when compared with the 6-31G* but not with the MP2/6-31G* interaction energy. The computed interaction enthalpy at the 6-31G* and MP2/6-31G* levels are −5.26 and −7.81 kcal/mol, respectively. The calculated entropy value is −26.66 eu and this leads to interaction free energies of 2.69 and 0.14 kcal/mol, respectively. The AM1 and PM3 values are even smaller than the interaction energies predicted for methanol. This does not make sense because methylamine is a stronger base than methanol. The *ab initio* methods, on the other hand, reproduce the expected ordering. This suggests that the semiempirical methods are not working well for nitrogen-based hydrogen bonding systems.[14]

Table XIV. Calculated interaction energies and interatomic distances for the methylamine–water complex (**38**).

Model	Energy (kcal/mol)	r(O—N) (Å)	r(N—H) (Å)
STO-3G	−5.66	2.907	1.918
3-21G	−10.40	2.877	1.900
6-31G*	−6.50	3.015	2.065
MP2/6-31G*	−9.05	2.902	1.942
PM3	−2.62	2.803	1.838
AM1	−3.00	3.132	2.707 (2.709)[a]

[a]The structure is bifurcated.

AM1 gives a bifurcated structure (**39**) that is not reproduced by the *ab initio* (**38**, see Fig. 6) and PM3 results.

N-Methylformamide–Water

Two hydrogen bonded complexes were studied, and the results are given in Table XV. This system has been studied previously, albeit at fixed geometries.[9,10] Although there is no direct experimental data for N-methylformamide–water interactions, the interaction enthalpies have been reported for several substituted amides.[10c] The values vary from −3.2 to −7.6 kcal/mol (the experimental errors also vary from compound to compound).[10c] Our calculated values are within this range.

All methods, except STO-3G, predict the complexes formed between the carbonyl oxygen of N-methylformamide and the hydrogen atom of the water molecule to be most stable (**42**). The computed interaction enthalpies for **40** and **42** using 6-31G* relative energies are −3.95 and −5.16 kcal/mol, respectively. Using MP2/6-31G* relative energies, the interaction enthalpies are −5.88 and −7.29 kcal/mol, respectively. While we do not have any direct experimental evidence for this complex, our computed interaction enthalpies are in the range observed for other substituted amides (−3.2 to −7.6 kcal/mol). The computed interaction entropies for **40** and **42** are −18.51 and −25.51 eu, respectively. The resulting interaction free energies for **40** and **42** using 6-31G* (MP2/6-31G*) energies are 1.57 kcal/mol (−0.36 kcal/mol) and 2.45 kcal/mol (0.32 kcal/mol), respectively. Hence, it appears likely that all of the structures are not stable on the free energy surface at 298.15 K.

The AM1 calculated interaction energies are in good agreement with the 6-31G* values, while the MP2/6-31G* values are about 2 kcal/mol more negative than both the 6-31G* and AM1 results. PM3 gives the smallest values of all methods and is in poor agreement with *ab initio* and AM1 results.

The geometries for the various N-methylformamide–water complexes are given in Figure 7. AM1 again gives bifurcated structures (**41** and **43**), while the MP2/6-31G* (**40** and **42**) and PM3 structures are similar except the hydrogen bond distance for the former is much shorter than the latter (see Table XV).

The poor performance of PM3 is this case can be rationalized by the fact that PM3 predicts too long hydrogen bond distances relative to all other methods. It is curious that it does so in this case because we have not seen this behavior in previous examples. However, this is the first carbonyl–water interaction we studied and it could be that PM3 is not able to handle these interactions well. We already observed that PM3 does not treat cases where nitrogen is involved in the hydrogen bonding interaction well and

Table XV. Calculated interaction energies and interatomic distances for the formamide–water complex.

Model	40[a]			42[b]		
	Energy (kcal/mol)	r(O—N) (Å)	r(O—H) (Å)	Energy (kcal/mol)	r(O—O) (Å)	r(O—H) (Å)
STO-3G	−5.87	2.778	1.745	−4.61	2.799	1.810
3-21G	−10.76	2.868	1.863	−11.94	2.729	1.878
6-31G*	−5.46	3.087	2.094	−6.99	2.899	2.012
MP2/6-31G*	−7.39	2.997	1.981	−9.12	2.854	1.941
PM3	−1.76	3.413	2.700	−3.82	3.138	2.608
AM1	−3.5	2.997	2.225	−5.02	2.684	2.218 (2.220)

[a]Methyl formamide as donor.
[b]Methyl formamide as acceptor.

this is again confirmed in this case. AM1 again gives bifurcated structures (**41** and **43**). Finally, it is interesting to note that both PM3 and STO-3G predict a nonplanar configuration around the nitrogen center.

We also investigated the interaction between two N-methylformamide molecules (**44**). This is a good model for interchain O—H-N interactions. Because formamide tends to form a cyclic dimer,[10] we decided to use N-methylformamide instead. The calculations were carried out with STO-3G and AM1 only. The calculated interaction energy and interaction enthalpy are −4.7 and −4.2 kcal/mol, respectively. The self-association of methylformamide has been measured using nuclear magnetic resonance (NMR) techniques in CCl_4 and dioxane.[40] In

CCl_4, the experimental interaction enthalpy value is −3.7 ± 0.3 kcal/mol. It is clear that both AM1 and STO-3G work well in this case. This is maybe not surprising because both STO-3G and AM1 gave interaction enthalpies in reasonable agreement with the 6-31G* calculations for **40** and **42**. More sophisticated calculations would have been more instructive, but they were found to be too costly.

Formic Acid-13a and Formate-14a Interactions

The interaction between formate (**9**) and **14a** is a model for one of the salt–bridge interactions present in proteins. There are two structures: The first can be viewed as a neutral hydrogen bonded complex between formic acid (**8**) and **13a** and the second is zwitterionic and results from the combination of formate (**9**) and **14a**. We examined both of these possibilities. The calculations were only done up to the 6-31G* level due to the size of the system.

The interaction energies in Table XVI follow the same trend we have seen for other neutral–neutral systems. Although no direct experimental information is available in this case or for the next one, there is data available for neutral carboxylic acid and amide dimers.[10b,10c] The interaction enthalpy is usually in the −14 to −15 kcal/mol range.[10b,10c] Using this range of interaction enthalpies as an approxi-

(40)

(42)
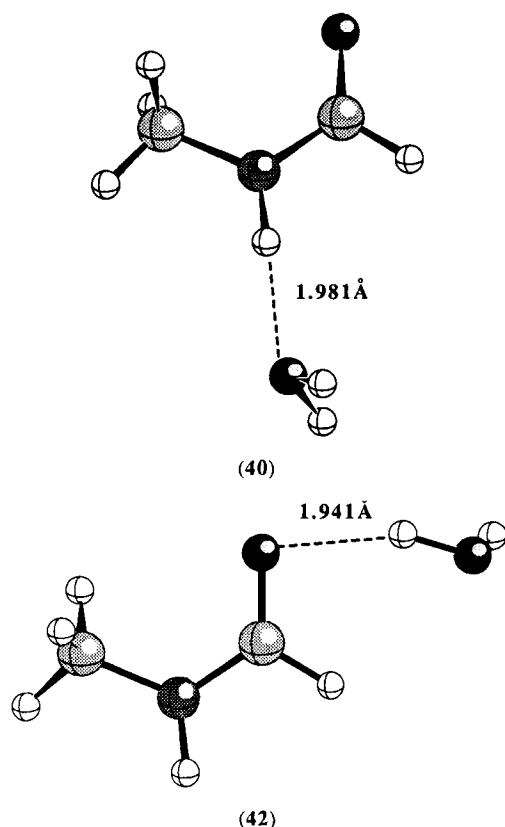
Figure 7. Calculated MP2/6-31G* (**40** and **42**) geometries.

Table XVI. Calculated interaction energies and interatomic distances for **45**.

Model	Energy (kcal/mol)	r(C—C) (Å)	r(N—O) (Å)[a]
STO-3G	−15.77	3.876	2.695
			2.615
3-21G	−29.24	3.911	2.830
			2.578
6-31G*	−16.17	4.109	3.045
			2.792
PM3	−8.68	4.097	2.745
			2.831
AM1	−3.41	4.448	3.089
			3.309

[a]The first value refers to the O—H-N hydrogen bond while the second refers to the O-H—N hydrogen bond.

mation for the true value for the formation of the neutral dimer (**45**; see Figure 8), we find that the AM1 and PM3 values are clearly too small (see Table XVI). To estimate the thermodynamic corrections for this case, we used 6-31G* vibrational frequencies, which results in a prediction of an interaction enthalpy of − 14.6 kcal using 6-31G* energies. This value is in good agreement with the range observed for the neutral carboxylic acid and amide dimers. The computed entropy is − 34.1 eu, which gives an interaction free energy of − 4.4 kcal/mol at 298 K. Hence, this complex is predicted to be stable on the free energy surface.

The data for the zwitterionic structure (**47**; see Figure 8) is given in Table XVII. At the 6-31G* level of theory, the zwitterionic structure is not a minimum on the potential energy surface and was only obtained by enforcing symmetry in the calculation. For the semiempirical and low-level *ab initio* calculations, the zwitterionic structure was found to be a minimum. The low-level *ab initio* methods clearly give interaction energies that are too negative. The stabilization of the zwitterion with respect to two separated ions is large. Both AM1, PM3, and *ab initio* methods predict a stabilization energy of over 100 kcal/mol (at the 6-31G* level, the stability of **47** relative to **9** and **14a** is 125.3 kcal/mol).

According to our calculations, the neutral structure is more stable in the gas phase. AM1 (PM3) predicts a 16.7 kcal/mol (16.1 kcal/mol) energy difference between the neutral (**45**) and zwitterionic (**47**) case, while at the 6-31G* level the energy difference is only 5 kcal/mol (see total energies given in Table I). Based upon this, we conclude that the energy difference between **45** and **47** is relatively small and that the potential energy surface at the 6-31G* level is relatively flat. Moreover, larger basis sets or inclusion of correlation might further reduce this difference (see next section).

The geometry of **45** has some interesting features. First, the hydrogen bonds are asymmetric (see Table XVI), with the O—H-N distance being longer than that of O-H—N for the *ab initio* calculations. The semiempirical results give the exact opposite trend.

Table XVII. Calculated interaction energies and interatomic distances for **47**.

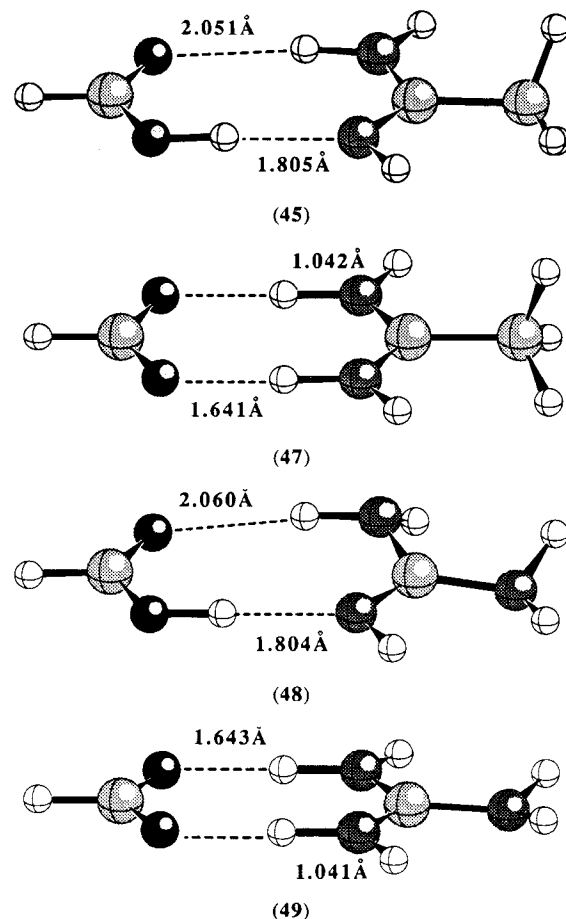| Model	Energy (kcal/mol)	r(C—C) (Å)	r(N—O) (Å)
STO-3G	− 193.6	3.634	2.402
			2.402
3-21G	− 143.7	3.801	2.600
			2.600
6-31G*	− 125.3	3.871	2.684
			2.684
PM3	− 121.5	3.994	2.697
			2.697
AM1	− 109.6	3.941	2.782
			2.782

Figure 8. Calculated 6-31G* (**45**, **47**, **48**, and **49**) geometries.

Second, the semiempirical methods predict the amide group to be nonplanar, which is at variance with the *ab initio* results.

Formic Acid-13b and Formate-14b Interactions

Previous calculations on the interaction of **9** with **14b** were carried out with small basis sets and under geometric constraints.[10,11-13] Because it has been shown that relaxation of all geometric variables is very important to get a reasonable energy for the carboxylic acid dimer,[41] it is necessary to check this system again. Also, for the zwitterionic complex polarization functions may play an important role. For this set of calculations, we only employed the 6-31G*, AM1, and PM3 methods in conjunction with guess geometries built from the results of the calculations given in the previous section. We have not employed the smaller basis sets in this case because we felt that the information would mirror that found for **45** and **47**. The results for these two systems are given in Tables XVIII and XIX. Thermodynamic corrections were computed at the 6-31G* level, and both the neutral complex (**48**) and the zwitterion (**49**) were

Table XVIII. Calculated interaction energies and interatomic distances for **49**.

Model	Energy (kcal/mol)	r(C—C) (Å)	r(N—O) (Å)
6-31G*	−16.37	3.677	2.485 2.482
PM3	−7.30	4.097	2.744 2.829
AM1	−5.25	4.371	2.974 3.355

characterized to be minima on the 6-31G* potential energy hypersurface (see Figure 8).

Previous constrained 6-31G calculations[12] predicted an energy difference of 11.86 kcal/mol between **48** and **49** favoring **48**. At the 6-31G* level, the energy difference is only about 5 kcal/mol. Clearly, the polarization function is important here and, furthermore, relaxation of all geometrical parameters might have also had some effect. Earlier DZ calculations[13] did give a small energy difference, but again due to applied geometric constraints the results have to be viewed with caution. It may be possible that at higher levels the difference between **48** and **49** could become even smaller. In fact, a single point calculation at the MP2/6-31G*//6-31G* level reduces the energy difference to 3.2 kcal/mol. The interaction enthalpy for the formation of **49** is again quite large, being −121.5 kcal/mol at the 6-31G* level. For **48**, the interaction enthalpy is 18.9 kcal/mol at the 6-31G* level, bigger than that observed for **45** and for the amide and carboxylic acid dimers.[10b,10c] The free energy differences between **48** and **49** are 3.64 and 1.84 kcal/mol at the 6-31G* and MP2/6-31G* levels, respectively. The semiempirical methods do not reproduce the 6-31G* interaction enthalpy for the formation of **48**, while PM3 matches the 6-31G* result for the formation **49** much better than does AM1.

It is clear from Tables XVI–XIX that replacement of the methyl group by an electron-donating group such as NH$_2$ causes a modest change in geometry for both the neutral and zwitterionic species. We find that replacement of the CH$_3$ group with NH$_2$ causes the complexes to become nonplanar (**48** and **49**), while in the monomer (**14b**) is planar. This nonplanarity is especially pronounced in the case of neutral complex **48**. Besides these differences, we find that the NH$_2$ and CH$_3$ complexes are similar in many ways (e.g., hydrogen bond lengths).

Methylamine–Formic Acid

Formic acid has two isomeric structures: *syn* and *anti*. It has been shown by Li and Houk[42] that the hydrogen bonded complex formed between ammonia and the *syn* acid is more stable than that formed with the *anti* acid by about 6 kcal/mol and, therefore, we will ignore the *anti* case here. The calculated results are shown in Table XX. As reported previously,[11b] the zwitterionic form is unstable (**52**). The zwitterionic form was obtained by imposing symmetry and at the 6-31G* level our calculated energy difference is 21.2 kcal/mol between **52** and **50**.

The energetic results for the neutral case (**50**) follow the same pattern of STO-3G, being close to 6-31G* and 3-21G being the most negative. Inclusion of correlation at the MP2/6-31G* level increases the interaction energy by almost 4 kcal/mol over 6-31G*. The calculated enthalpies at the 6-31G* and MP2/6-31G* levels are −9.62 and −14.43 kcal/mol, respectively, for the neutral hydrogen bonded complex. The calculated entropy is −29.93 eu, which results in interaction free energies at 298.15 K of −0.7 and −5.5 kcal/mol, respectively. AM1 and PM3's interaction enthalpies are too small by a factor of 3 or 4. In this case, the *ab initio* and semiempirical geometries (Fig. 9) are in reasonable accord except for AM1 (**51**), which gives a hydrogen bonding distance that is too long.

Imidazole and Protonated Imidazole With Water

Imidazole can act as both an acceptor and a donor; therefore, there are two possible hydrogen bonded complexes (**53** and **55**). Imidazole–water interactions have been studied by others using fixed geometries at the 4-31G level of approximation,[43] but we decided to extend the study of this system to more sophisticated levels. The present results are summarized in Table XXI. Correcting the interaction energies for **53** and **55** yields interaction enthalpies at the 6-31G* (MP2/6-31G*) level of −5.25 kcal/mol

Table XIX. Calculated interaction energies and interatomic distances for **48**.

Model	Energy (kcal/mol)	r(C—C) (Å)	r(N—O) (Å)
6-31G*	−122.9	3.877	2.682 2.682
PM3	−119.6	3.965	2.697 2.696
AM1	−108.2	3.860	2.751 2.783

Table XX. Calculated interaction energies and interatomic distances for **50**.

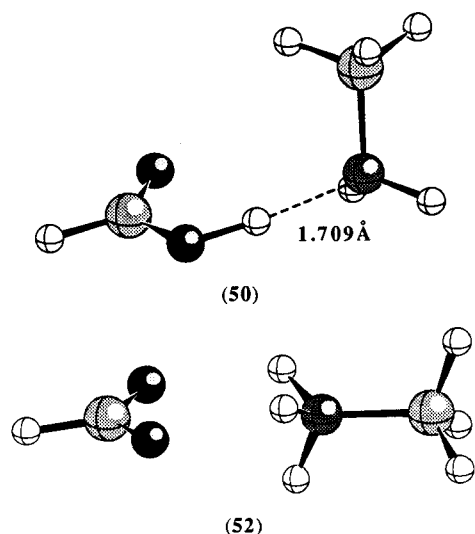| Model	Energy (kcal/mol)	r(N—O) (Å)	r(N—H) (Å)
STO-3G	−10.53	2.706	1.704
3-21G	−20.12	2.666	1.650
6-31G*	−11.45	2.834	1.871
MP2/6-31G*	−16.26	2.718	1.709
PM3	−4.73	2.764	1.787
AM1	−2.75	3.444	2.486

Figure 9. Calculated MP2/6-31G* (50 and 52) geometries.

Figure 10. Calculated MP2/6-31G* (53, 55, and 57) geometries.

(−7.88 kcal/mol) and −4.83 kcal/mol (−7.10 kcal/mol), respectively. The calculated entropies for 53 and 55 are −26.04 and −19.83 eu, respectively, and the resulting free energies of interaction at the 6-31G* (MP2/6-31G*) levels are 2.51 kcal/mol (−0.12 kcal/mol) and 1.08 kcal/mol (−1.19 kcal/mol), respectively. Thus, MP2/6-31G* predicts that both 53 and 55 are stable on the free energy surface, while 6-31G* predicts the opposite. PM3 and AM1 both give interaction enthalpies that are ~2-3 kcal/mol too small relative to the 6-31G* interaction enthalpies, while the agreement is even worse when compared to the MP2/6-31G* values. Another feature of note is the stability order for these two complexes. The best ab initio methods and PM3 tend to favor 53 over 55, while AM1, STO-3G, and 3-21G favor 55.

The ab initio methods and PM3 give a normal hydrogen bonded complex for 53, but AM1 gives the bifurcated structure 54. For 55, AM1 is similar to the other methods but the water molecule is oriented parallel to the imidazole ring (56), while the other methods place it perpendicular (55). Structures 53, 55, and 57 are given in Figure 10.

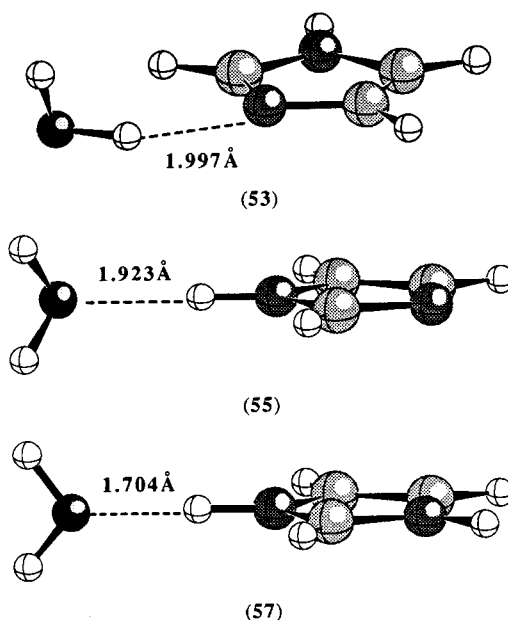The interaction between protonated imidazole and water has also been investigated using both semi-

empirical and ab initio molecular orbital methods. The calculated results, together with the experimental result, are given in Table XXII.[44] The calculated interaction enthalpy using 6-31G* and MP2/6-31G* energies is −15.37 and −18.69 kcal/mol, respectively. It is interesting to note that earlier fixed geometry results agree quite well with our fully optimized results as far as the interaction energy and interatomic N—O distance is concerned.[45] The calculated entropy is −25.57 eu, which yields free energies of interaction of −11.07 and −7.75 kcal/mol. The 6-31G* interaction enthalpy is in excellent agreement with the experimental value of −14.8 kcal/mol, while the MP2/6-31G* value is too negative by about 3 kcal/mol. This trend is similar to the methyl ammonium case described above. The semiempirical methods both give values that are too positive by ~4 kcal/mol. Again, this is a hydrogen bonded system that involves nitrogen and again the match with both ab initio and experimental results is not good.

The ab initio and PM3 methods give a normal hydrogen bonded complex (56), while AM1 again

Table XXI.   Calculated interaction energies and interatomic distances for the imidazole–water complex.

Model	53[a]			55[b]		
	Energy (kcal/mol)	r(N—O) (Å)	r(N—H) (Å)	Energy (kcal/mol)	r(N—O) (Å)	r(O—H) (Å)
STO-3G	−5.56	2.940	1.954	−10.15	2.638	1.595
3-21G	−11.87	2.797	1.964	−12.58	2.798	1.789
6-31G*	−7.06	2.972	2.101	−6.37	3.029	2.030
MP2/6-31G*	−9.69	2.884	1.997	−8.64	2.944	1.923
PM3	−3.37	3.340	1.823	−3.23	2.823	1.824
AM1	−2.90	3.167	2.719	−4.0	3.094	2.107
			(2.844)			

[a]Imidazole as hydrogen bond acceptor.
[b]Imidazole as hydrogen bond donor.

Table XXII. Calculated interaction energies and inter-atomic distances for the protonated imidazole–water complex (**57**).

Model	Energy (kcal/mol)	r(N—O) (Å)	r(H—O) (Å)
STO-3G	−29.72	2.439	1.312
3-21G	−27.29	2.627	1.584
6-31G*	−16.95	2.819	1.806
MP2/6-31G*	−20.27	2.745	1.704
PM3	−10.76	2.776	1.774
AM1	−10.70	2.820	2.253 (2.283)[a]
Experimental	−14.8		

[a]This is the distance between O and one of the C—H hydrogen atoms.

gives a bifurcated structure (**57**) where the oxygen is interacting with an adjacent imidazole C—H hydrogen atom. This has been observed and described previously.[46]

CONCLUSIONS

High-level *ab initio* molecular orbital calculations were used to study hydrogen bonding interactions in a number of model compounds closely related to hydrogen bonding patterns present in proteins. For all but the phenolate–water case, thermodynamic information was calculated using vibrational frequencies determined at the 6-31G* level. High-level *ab initio* calculations reproduce the limited experimental values reasonably well and many of the trends we see in energies and structure relative to the level of sophistication agree with what has already been observed by a number of authors.[5-13,26] We summarize these trends below.

For the energetics of the neutral complexes, we find that STO-3G is in reasonable accord with interaction energies computed using the 6-31G* basis set, while the 3-21G interactions energies are usually much more negative. Inclusion of correlation at the MP2/6-31G* level results in interaction energies that are significantly more negative than the 6-31G* values but not as negative as the 3-21G values. The geometries of the hydrogen bonds in the neutral complexes show some definite trends. The 6-31G* hydrogen bond distance is the longest for all of the basis sets we used and inclusion of correlation at the MP2/6-31G* level always results in a bond distance shorter than that obtained at the 6-31G* level. The STO-3G and 3-21G hydrogen bond distances are usually the shortest, but sometimes the MP2/6-31G* distance is shorter. Finally, the variation in the hydrogen bond distance among the various basis sets in the ±0.1 to ±0.2 Å range.

The energetic trends for the anionic complexes are different than those found for the neutral compounds. We find that as the basis set was increased the interaction energy decreased significantly. Inclu-

sion of correlation at the MP2/6-31 + G* level did decrease the interaction energy over the 6-31 + G* value significantly and the best agreement with experiment was obtained at the former level and not the latter. Furthermore, inclusion of the diffuse function was needed to get the best match with experiment as has been described by others.[6,7,8f] The phenolate–water system, however, gave a trend that was more like the neutral–neutral cases than the other anion–neutral systems. This could be due to delocalization of the negative charge into the π system of the benzene ring, which would reduce the charge concentration at the oxygen atom. The geometric trend for the anionic–neutral complexes is similar to that of the neutral–neutral complexes. The 6-31 + G* level gives the longest hydrogen bonding distance and the STO-3G and 3-21G the shortest. MP2/6-31 + G* calculations give hydrogen bond distances intermediate between the small and large basis set calculations.

The energetic trend for the cation–neutral systems is similar to that for the anion–neutral cases, but we find that the best agreement with experiment is obtained at the 6-31G* level and not at the MP2/6-31G* level. This trend is more like that expected for the neutral–neutral cases. The trend in the hydrogen bonding distances is also like that for the anion–neutral cases.

The various trends observed in the *ab initio* calculations described above are due to a complex mixture of factors. Fortuitous cancellation of errors (e.g., the error in the monomer energies is cancelled by an opposite error in that of the hydrogen bonded complex) is probably responsible for the observation that STO-3G and 6-31G* give good interaction energies while 3-21G and MP2/6-31G* do not. BSSE is also involved in the observed trends and assessing the magnitude of its role is the subject of significant controversy.[20-23] Unravelling the role of these various factors will continue to be of significant interest in the future.[20-23]

We also carried out semiempirical molecular orbital calculations. Many previous calculations have indicated that semiempirical interaction enthalpies are lower than the corresponding interaction energies obtained using *ab initio* methods.[14,28] However, this is not the best way in which to compare these methods because one is an interaction enthalpy and the other an interaction energy. To solve this, we converted the *ab initio* interaction energies into interaction enthalpies. In general, we find that the *ab initio* interaction enthalpies are less than the corresponding interaction energies. This has the effect of bringing the semiempirical and *ab initio* results into better accord than has been observed previously.[14,28] However, the AM1 and PM3 interaction energies are in general too low.[14,28] Furthermore, AM1 tends to favor a bifurcated structure for the O—H-O and N—H-O types of hydrogen bonds.[14b,28]

This is not true in cases where sulfur is involved in the hydrogen bond interaction. Therefore, AM1 is not suitable for calculating interatomic distances in these hydrogen bonded complexes. In contrast to AM1, PM3 geometries are quite good when compared to the *ab initio* results and the PM3 interaction energies are similar to the AM1 values in most cases.[14a,18] From this point of view, PM3 does show some improvement over AM1. Finally, we note that our analysis of PM3 and AM1 hydrogen bonding complexes is the most extensive to date.[14a,18]

A strong trend that came out of this work with regard to the capabilities of the semiempirical methods is the observation that nitrogen-based hydrogen bonding systems are not well reproduced by either PM3 or AM1. Rzepa and Yi have seen this same problem in ammonia complexes.[14a] This suggests that future parametrization efforts should pay closer attention to these systems to alleviate this situation.

Semiempirical methods like AM1 and PM3 are much better at handling hydrogen bonding than were their precursors. However, it is clear that there is room for improvement. Clearly, PM3 has improved geometries over AM1, but neither method give interaction energies that appear to be strong enough. One of the major drawbacks in developing parametric methods like AM1 and PM3 is the lack of an extensive data base of accurate interaction energies and geometries for hydrogen bonded complexes. Efforts like this one represent an attempt to alleviate this problem. Future studies at more sophisticated levels will start to build up the necessary level of information needed to obtain a semiempirical method that gives accurate representations of hydrogen bonded systems.

Molecular mechanical methods can also greatly benefit from collections of this sort. The information presented here can be used to develop molecular mechanical parameters that reproduce hydrogen bonding interactions at the level of sophistication used here. Parameters derived in this way can then be tested in their ability to reproduce other experimental information, such as condensed phase properties, etc.[2a]

An interesting debate has surrounded the formate–water system with regard to the minimum energy structure. One is the cyclic complex **33** and the other the open structure **34** (see Fig. 4). Experimentally, Meot-Ner suggested that **34** is favored over **33** based upon the fact that both water and methanol give similar interaction enthalpy. However, our results suggest that the latter is enthalpically favored by 3.2 kcal/mol at the MP2/6-31G* level. We also find that this trend holds for the formate–methanol system, which favors a cyclic structure **33'** (see Fig. 5) over the open one (**34'**) by 1.7 kcal/mol. This trend is also present on the free energy surface but to a lesser extent. The interaction enthalpies for the

open structures we obtain are in the best agreement with Meot-Ner's experimental data, which suggests to us that the open structure is being observed. Furthermore, Meot-Ner[35] suggested that the closed structure is not observed due to entropy considerations. Our calculated entropies do agree with this conclusion because the entropy for the open structure is more favorable than for the closed one.

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