HEATS OF FORMATION OF ORGANIC MOLECULES BY *AB INITIO* CALCULATIONS. 1. ALIPHATIC AMINES

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A bond energy scheme has been developed and two previously existing schemes have been extended for the calculation of heats of formation of aliphatic amines using *ab initio* 6–31G* energies in place of experimental data. The results are in good agreement with those obtained experimentally and suggest that this method can be used to predict heats of formation of molecules of this class with an accuracy competitive with good quality experiments, and with probable errors of less than 1 kcal mol^{-1}.

INTRODUCTION

The heat of formation is an important parameter of a compound and has traditionally been determined by heat of combustion measurements. There is a large body of data on heats of formation for hydrocarbons,[1] determined primarily by this method. For hydrocarbons substituted with a simple functional group, such as amines, there are fewer experimental data, and they are not always of high accuracy. Heat of combustion work has not been very fashionable for many years, and there are available many interesting compounds for which the heats of formation have not been determined. The prognosis is that this situation will continue to deteriorate, which suggests that reliable calculated values for heats of formation would be highly desirable. In addition, often one would like to have heat of formation data on compounds that are not available for experimental measurements.

The difficulty in trying to calculate heats of formation by *ab initio* methods directly is well known.[2] Because the energies which result when electrons and nuclei are put together are so large, even small percentage errors amount to many kcal mol^{-1}. However, if instead of using absolute numbers on compares isodesmic reactions, so that the number and kinds of bonds and structural features remain constant, then most of the error cancels out, and one can obtain reasonable estimates for heats of formation. Another approach, which is a variant of the same idea, is to determine empirically a set of group or atom equivalents which when added to the *ab initio* energy yields the heat of formation. This technique has previously been studied independently by Wiberg[3] and Ibrahim and Schleyer.[4] Both groups found that the heats of formation of hydrocarbons could be calculated with an rms error of about 1 kcal mol^{-1} when the 6–31G* basis set was used. For other functional groups, the errors were slightly greater, although the data sets used were small.

Hydrocarbons are more or less ideal compounds for *ab initio* calculations. One would like to know how accurately the heats of formation can be determined for classes of compounds which contain lone pairs, of which the amines constitute a simple example. In this work, we have extended the schemes of Wiberg and Ibrahim and Schleyer to include aliphatic amines. Ibrahim and Schleyer included atom equivalents for nitrogen compounds in their work. However, these were derived from a set of compounds that included a variety of nitrogen containing functional groups, and the set contained only three amines. We felt that more useful results could be obtained by limiting the parameters to amines and including a much wider selection of compounds.

Additionally, we have developed our own set of

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equivalents for alkanes and amines based on the same set of structural elements used in the MM2 and MM3 bond increment schemes. Like its molecular mechanics counterpart, our *ab initio* scheme explicitly includes the statistical mechanical terms[5] POP (the energy resulting from populating higher energy conformations of the molecule), TORS (the energy resulting from populating low-lying vibrational states) and T/R (the energy terms required to convert ΔE to ΔH and to account for the translational and rotational motion of the molecule). The inclusion of these terms is conceptually an improvement over the previous work in which these terms were not explicitly included, and were therefore compensated for in the parameters themselves. Rigorous determination of these statistical mechanical terms is difficult and these quantities are often not available. They can, however, be estimated[5] and it has been our experience with molecular mechanics that doing so will improve the quality of results, particularly for larger molecules.

There was one other question that we wanted to answer. In our molecular mechanics study on the heats of formation of amines, there appeared to be a significant problem with diisopropylamine. The experimental value for the heat of formation of this compound was reproduced poorly in our MM3 calculations. It was not completely clear if the fault lay with the experimental value for this compound, with experimental errors in other compounds which just happened to yield this result, or if this was a problem in molecular mechanics. Our thought was that if the experimental heat of formation for diisopropylamine contains a sizeable error, then the *ab initio* value should agree with the MM3 value and not with the experimental value. On the other hand, agreement of the *ab initio* value with experiment would indicate that the error was in the molecular mechanics calculations.

COMPUTATIONAL METHODS

All of the increments and *ab initio* energies reported in this paper are based on calculations using the 6–31G* basis set.[6] The required *ab initio* energies for the alkanes were taken from the tabulations of Wiberg and Ibrahim and Schleyer. For methylamine, the energy was taken from the Carnegie–Mellon Quantum Chemistry Archive.[7] The 6–31G* energy of propylamine was reported by Schmitz *et al.*[8] Values for the remaining amines were calculated using a Cray-XMP super computer running GAMESS.[9] The geometry optimizations were done by first running a few cycles of optimization using the Schlegel algorithm,[10] followed by the Baker procedure[11] until the largest component of the gradient was less than 4×10^{-4} hartree bohr^{-1}. In the case of triethylamine, the largest component of the gradient was $5 \cdot 95 \times 10^{-4}$ hartree bohr^{-1} with an rms gradient of

$2 \cdot 05 \times 10^{-4}$ hartree bohr^{-1} for the final structure. Tests showed that the likely error from gradients of this size were less than $0 \cdot 1$ kcal mol^{-1}.

The POP terms required for the molecular mechanics style group equivalents scheme were estimated by using the usual procedure[5] and relative energies of the conformations as calculated by molecular mechanics rather than by *ab initio* calculations. The TORS terms were estimated using the assumption that this term arises from the population of low-energy rotational modes. Therefore, as has been our practice with MM3, for each bond around which there is relatively free rotation (barrier less than 7 kcal mol^{-1} and excluding methyl groups) a contribution of $0 \cdot 42$ kcal mol^{-1} ($0 \cdot 00067$ hartree) to TORS was assigned. The T/R terms was taken to be $4RT$ or $2 \cdot 4$ kcal mol^{-1} ($0 \cdot 00382$ hartree) for nonlinear molecules.

RESULTS AND DISCUSSION

Alkanes

Nine relatively unstrained compounds were chosen to determine the equivalents for the alkanes. The group equivalents determined were for the carbon—carbon and carbon—hydrogen bonds and the methyl (Me), isopropyl (ISO) and neopentyl (NEO) groups. A least-squares fitting of the appropriate data yielded the equivalents in Table 1. The conversion of an *ab initio* energy to heats of formation then can be done according to the equation

$$\Delta H_f = \Delta E_{6-31G^*} + POP + TORS + T/R + \Sigma (n \times \text{equivalent})$$

where n equals the number of occurrences of the equivalent in the molecule, the summation is over all equivalents and ΔE_{6-31G^*} is for the lowest energy conformer of the molecule. The heat of formation for any particular conformation can be calculated by setting POP to zero and using the appropriate *ab initio* energy. Table 2 compares the observed and calculated heats and presents the other data used in the calculations. The rms error over the set of nine compounds is only $0 \cdot 5$ kcal mol^{-1}.

Table 1. Bond and group equivalents for alkanes

Group	Equivalent (hartree)
Me	0·002423
Iso	−0·003879
Neo	−0·010139
C—C	18·944516
C—H	10·040710

Table 2. Data and results for alkanes[a]

Compound	Energy (hartree)				Energy (kcal mol^{-1})		
	POP	TORS	T/R	$\Delta E_{6-31G}*$	$\Delta H_{f(exp)}$	$\Delta H_{f(calc)}$	Diff.
Methane	0·0	0·0	0·00382	−40·19517	−17·89	−17·89	0·00
Ethane	0·0	−0·00067	0·00382	−79·22876	−20·04	−20·07	−0·03
Propane	0·0	0·0	0·00382	−118·26365	−25·02	−25·27	−0·25
n-Butane	0·00048	0·00067	0·00382	−157·29840	−30·03	−30·08	−0·05
Isobutane	0·0	0·0	0·00382	−157·29897	−32·07	−32·07	0·00
n-Pentane	0·00104	0·00134	0·00382	−196·33302	−35·08	−34·76	0·68
Neopentane	0·0	0·0	0·00382	−196·33383	−40·14	−40·14	0·00
Cyclopentane	0·0	0·0	0·00382	−195·16124	−18·44	−17·41	1·03
Cyclohexane	0·0	·0·0	0·00382	−234·20799	−29·50	−30·47	−0·97

[a] The *an initio* energies and heats of formation were taken from Ref. 3.

Amines

The parameterization for amines is based on 19 compounds. In addition, heats of formation are predicted for azetane, for which the heat of formation is not known, and for diisopropylamine, which was not included in the fitting since we now believe that the experimental heat of formation is in error (see below). We have derived three sets of equivalents, for use with the group equivalents of Wiberg, with the atom equivalents of Ibrahim and Schleyer and with the equivalents described above.
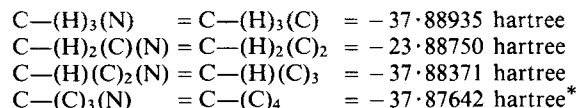
For the Wiberg group equivalents, we derived equivalents for the NH_2 group (primary amines), NH group (secondary amines) and N group (tertiary amines). The selection of this set of group increments is consistent with the philosophy of the original parameterization for alkanes in which the selected increments were for methyl, methylene, methine and quaternary carbon groups. The new set of equivalents are reported in Table 3.

In the case of the atom equivalent scheme, we have deviated slightly from the scheme originally presented by Ibrahim and Schleyer.[4] In the original scheme, the carbon attached to a heteroatom was always assigned a value equal to that of the increment for C—(H)$_3$(C). The original data set included only three amines, all of which had the amino nitrogen bound to methyl groups or primary carbons. The set of data included here contains amines in which the amino group is attached to methyl, primary, secondary and tertiary carbons. We

were able to obtain much better results by assigning different increments for the carbon bearing the amino group, based on the number of substituents at that carbon. Therefore, we used the published values for appropriately substituted alkane carbons for the carbon bearing the nitrogen as shown below:

C—(H)$_3$(N)   = C—(H)$_3$(C)   = −37·88935 hartree
C—(H)$_2$(C)(N) = C—(H)$_2$(C)$_2$ = −23·88750 hartree
C—(H)(C)$_2$(N) = C—(H)(C)$_3$ = −37·88371 hartree
C—(C)$_3$(N)   = C—(C)$_4$ = −37·87642 hartree*

For the atoms of the amino group, the H—(N) value (−0·56636 hartree) was retained as originally published. However, three new equivalents, N—(H)$_2$(C), N—(H)(C)$_2$ and N—(C)$_3$, the amine nitrogen in primary, secondary and tertiary amines, respectively, were derived. The resulting equivalents are reported in Table 4.

In MM3 eight equivalents are used for calculating the heats of formation involving amino groups. In this study we are able to use a subset of this group in which the two equivalents for cyclobutane rings are not included. Since the *ab initio* energy includes the strain in small rings, it is not necessary to include these terms. The six equivalents used are C—N (carbon—nitrogen bonds), N—H (nitrogen—hydrogen bonds), N—Me

Table 3. Equivalents of aliphatic amines for use with the Wiberg[3] scheme

Group	Equivalent (hartree)
NH_2	−55·603455
NH	−55·036376
N	−54·462817

Table 4. Equivalents for aliphatic amines for use with the Ibrahim and Schleyer[4] scheme

Atom	Equivalent (hartree)
N—(H)$_2$(C)	−54·466218
N—(H)(C)$_2$	−54·465522
N—(C)$_3$	−54·458497

* An equivalent for C—(C)$_4$ was not published. Therefore, we derived one from the heat of formation and 6—31G* energy for neopentane as given in Reference 3.

(nitrogen bond to a methyl group), NISO (nitrogen bond to a secondary carbon), NSEC (nitrogen bond to a secondary nitrogen) and NTBU (nitrogen bond to a tertiary carbon). The values of the equivalents for this scheme are reported in Table 5.

Tables 6 and 7 report the relevant input and output data, respectively, for calculating the heats of formation of amines, and compare the results of the calculations with experimental values. Overall, each of the schemes is able to reproduce the experimental data with an rms error that is competitive with the experimental error. Since the rms errors are close to the typical experimental errors for heats of formation, it cannot be concluded that the apparent superiority of the present scheme with statistical mechanical terms (rms error $0 \cdot 47$ kcal mol^{-1}) to the other two schemes (rms errors $0 \cdot 79$ and $0 \cdot 75$ kcal mol^{-1}) is real. However,

we note that the main reason for the lower error of the present scheme is the ability to fit triethylamine. This ability does depend on the presence of the statistical mechanical terms, since we found by deriving yet another scheme based on the same set of equivalents but without the statistical mechanical terms that it does not result in a scheme that fits triethylamine well. Further, if the equivalents for all three schemes are re-evaluated leaving triethylamine out of the fitting process, each scheme gives a similar results with an rms error of about $0 \cdot 5$ kcal mol^{-1}. Nevertheless, until ab initio calculations are available for larger molecules in which the statistical mechanical terms make a larger contribution and, perhaps, until we can estimate better the statistical mechanical terms themselves, it will remain difficult to demonstrate conclusively the importance (or lack of importance) of including these terms in schemes such as these.

Perusal of Table 7, using the presently developed method from Table 5, shows that there is only one discrepancy between calculation and experiment that is as large as 1 kcal mol^{-1}. Since there are other compounds in the table which are secondary amines (such as diethylamine), and compounds which contain a branching group, such as isopropylamine, it seems impossible that the molecular mechanics value for diisopropylamine can be very far wrong. In fact, it agrees with the value calculated from the ab initio data

Table 5. Bond and group equivalents for aliphatic amines

Group	Equivalent (hartree)
C—N	27·627246
N—H	18·723018
N—Me	0·002481
NISO	−0·003461
NSEC	0·002217
NTBU	−0·005353

Table 6. Data for aliphatic amines

Compound	Energy (hartree)				Energy (kcal mol^{-1})
	POP	TORS	T/R	$\Delta E_{6-31G}*$	$\Delta H_{f(exp)}$[a]
Methylamine	0·00000	0·00000	0·00382	−95·20983	−5·50
Dimethylamine	0·00000	0·00000	0·00382	−134·23885	−4·43
Trimethylamine	0·00000	0·00000	0·00382	−173·26930	−5·67
Ethylamine	0·00005	0·00067	0·00382	−134·24773	−11·35
n-Propylamine	0·00038	0·00134	0·00382	−173·28248	−16·77
n-Butylamine	0·00094	0·00201	0·00382	−212·31708	−21·98
tert-Butylamine	0·00000	0·00067	0·00382	−212·32180	−28·90
Piperidine	0·00016	0·00000	0·00382	−250·18870	−11·76
2-Methylpiperidine	0·00025	0·00000	0·00382	−289·22679	−20·19
Cyclobutylamine	0·00038	0·00134	0·00382	−211·12142	9·90
Cyclopentylamine	0·00024	0·00134	0·00382	−250·18540	−13·13
Cyclohexylamine	0·00038	0·00067	0·00392	−289·23035	−25·06
Diethylamine	0·00075	0·00134	0·00382	−212·31404	−17·33
sec-Butylamine	0·00051	0·00134	0·00382	−212·31906	−25·06
Isobutylamine	0·00043	0·00134	0·00382	−212·31728	−23·57
Isopropylamine	0·00018	0·00067	0·00382	−173·28567	−20·02
Diisopropylamine	0·00011	0·00134	0·00382	−290·38362	−34·41
Pyrrolidine	0·00022	0·00067	0·00382	−211·14426	−0·80
Azetane	0·00005	0·00067	0·00382	−172·07865	—
Quinuclidine	0·00000	0·00000	0·00382	−327·07880	−1·03
Triethylamine	0·00010	0·00201	0·00382	−290·36962	−22·17

[a] Data from Ref. 1.

Table 7. Results for aliphatic amines

Compound	Heat of formation ($kcal\,mol^{-1}$) from						
	Exp.	Table 3	Diff.	Table 4	Diff.	Table 5	Diff.
Methylamine	−5·50	−5·03	0·47	−5·10	0·40	−5·10	0·40
Dimethylamine	−4·43	−3·61	0·82	−4·10	0·33	−3·82	0·61
Trimethylamine	−5·67	−7·15	−1·48	−7·54	−1·87	−6·22	−0·55
Ethylamine	−11·35	−12·11	−0·76	−12·04	−0·69	−12·19	−0·84
n-Propylamine	−16·77	−17·21	−0·44	−17·00	−0·23	−17·09	−0·32
n-Butylamine	−21·98	−22·22	−0·24	−21·87	0·11	−21·76	0·22
tert-Butylamine	−28·90	−27·81	1·08	−29·46	−0·56	−28·90	0·00
Piperidine	−11·76	−12·06	−0·30	−11·86	−0·10	−12·44	−0·68
2-Methylpiperidine	−20·19	−20·12	−0·07	−20·14	0·05	−20·66	−0·47
Cyclobutylamine	9·90	9·66	−0·24	9·93	0·03	10·65	0·75
Cyclopentylamine	−13·13	−13·79	−0·66	−13·72	−0·24	−13·31	−0·18
Cyclohexylamine	−25·06	−25·29	−0·23	−24·74	0·32	−25·57	−0·51
Diethylamine	−17·33	−17·82	−0·49	−17·60	−0·27	−17·23	0·10
sec-Butylamine	−25·06	−24·32	0·73	−24·33	0·73	−24·34	0·72
Isobutylamine	−23·57	−23·11	0·36	−23·21	0·36	−23·53	0·04
Isopropylamine	−20·02	−20·08	−0·06	−20·22	−0·20	−20·29	−0·27
Diisopropylamine	−34·41	−29·37	5·04	−30·01	4·40	−30·02	4·39
Pyrrolidine	−0·80	−0·88	−0·08	−0·82	−0·02	−0·37	0·43
Azetane	NA	23·59	NA	23·51	NA	24·42	NA
Quinuclidine	−1·03	−1·73	−0·70	−1·37	−0·34	−0·50	0·53
Triethylamine	−22·18	−19·99	2·19	−19·97	2·21	−22·17	0·01
Rms error excluding diisopropylamine			0·79		0·75		0·47

in this work to within an error of $1\cdot65\,kcal\,mol^{-1}$. On the other hand, the experimental value for diisopropylamine differs from the *ab initio* value by $4\cdot39\,kcal\,mol^{-1}$. We therefore conclude that the experimental value is in error, and hence have not weighted it in the parameterization.

We were interested in the heat of formation of azetane for the MM3 work, and no experimental value for that compound exists. We believe that the calculated value of $24\cdot42\,kcal\,mol^{-1}$ given in Table 7 should be reliable to within about $1\cdot0\,kcal\,mol^{-1}$.

CONCLUSION

Three combined empirical – *ab initio* schemes for calculating the heats of formation of amines have been shown to perform with a level of accuracy that is competitive with experimental measurements. The experimental heat of formation of diisopropylamine appears to be in error by about $4\,kcal\,mol^{-1}$.

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