Calculation of Formal Steric Enthalpy with MM2

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Steric energies calculated by molecular mechanics are used to estimate enthalpies of formation and differences and double differences of enthalpies of formation. The underlying principles and the precautions necessary to obtain valid results are analyzed. To compare results of calculations with two different force fields SE values are of little use, but they may be normalized to formal steric enthalpy (FSE) values which do provide a direct and unbiased comparison. Procedures are described for calculating FSE values with the MM2 and MM3 force fields. It is strongly recommended that results of molecular mechanics calculations be reported in terms of FSE values so that calculations in different laboratories with the same or with different force fields may be directly compared.

Introduction

The purpose of the present study is to examine the principles that underlie the use of SE values obtained by molecular mechanics to estimate differences and double differences of enthalpies of formation. A second purpose is to derive procedures for calculating FSE values with the MM2 and MM3 force fields so that results obtained with these force fields may be reported in a transferable form that permits direct comparisons with calculations performed with other force fields.

Molecular mechanics is a procedure for estimating an energy component of a particular geometry of a molecule along with a means to adjust the geometry so as to find conformers of minimum energy. The energy, defined in terms of an empirical force field, may be called the steric energy (SE) since it is in some sense a measure of steric "strain" that is due to the extent to which bonds, angles, and torsions depart from reference values, together with the sum of the resultant nonbonded interactions, eq 1.[1-15] The conformer of lowest energy, the global minimum, is of special importance.

$$SE = \sum\text{bonds} + \sum\text{angles} + \sum\text{torsions} + \sum\text{nonbonded} + \text{other terms} \quad (1)$$

The value of molecular mechanics lies in the fact that the steric energy can in principle provide an accurate estimate of a steric component of the enthalpy of formation. For certain compounds the steric energy of the global minimum may be converted to an estimate of the enthalpy of formation of the compound in the gas phase. More commonly differences of steric energies are used as estimates of differences of enthalpies of formation.

SE is not a well-defined measure of "strain" or of any other steric property since the value obtained depends on the details of the force field in use. This dependence can be removed by converting the SE value into the formal steric enthalpy (FSE), a quantity defined in terms of standard molecules.[16-23] FSE may be regarded as a normalized estimate of the steric component of the enthalpy of formation.

FSE values are unbiased and direct indicators of similarities and differences of force fields. Raw SE values are of little use for that purpose. By way of illustration, Table IIA of ref 16 lists SE and FSE values for alkanes as calculated with several force fields. The SE values show large divergences, and one force field even shows decreasing SE values with increasing steric crowding. Nevertheless, the FSE values are similar for all of the force fields, and the differences in FSE values are significant indicators of the different characteristics of the several force fields.

Enthalpies of Formation. It has long been known that enthalpies of formation can be represented as sums of increments together with a steric term, if necessary. Many expressions of this type have been proposed; the detailed treatment developed extensively by Benson, eq 2,[24-26] has proved especially useful.

$$\Delta H_f = \sum n_i b_i + \text{steric terms} \quad (2)$$

In this expression the b increments represent the contributions of structural elements to the bond energy component of the enthalpy of formation, so much per methyl group, so much per methylene, and so on. Benson provides

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tables of b increments for many types of structural elements and tables of typical steric terms. He uses 0.80 kcal/mol to represent the steric effect of each gauche interaction and various values for rings, 6.3 kcal/mol for a cyclopentane ring, for example.

Equation 2 embodies an important hypothesis, namely that the contribution to the enthalpy of formation due to any given structural element is independent of its position in a molecule. Any departure from additivity is to be attributed to the steric term. In other words, the difference (or discrepancy) $\Delta H_f - \sum n_i b_i$ is to be compensated by an appropriately chosen steric term.

Providing that the steric term can be unambiguously defined a priori, eq 2 provides a precise extrapolation of thermodynamic data.[27,28] Among the many variants of eq 2 are several based on extensions of the types of intramolecular interactions to be included and others that use extended sets of structural elements.[28-30] A limitation of all versions of eq 2 is that the steric term is treated as a stepwise quantity. The steps are usually too coarse for use of eq 2 in correlating rates and equilibria. A further limitation is that there are many compounds for which the steric term cannot be assigned a priori.

These limitations can, in principle, be overcome by estimating the steric term by use of molecular mechanics. Three expressions have been extensively used, eqs 3,[3,31] 4,[17,18,20-23] and 6.[1,8,10]

$$\Delta H_f = \sum n_i a_i + \mathrm{SE} + \mathrm{SM} \quad (3)$$

$$\Delta H_f = \sum n_i c_i + \mathrm{FSE} + \mathrm{SM} \quad (4)$$

$$\mathrm{FSE} = \mathrm{SE} - \sum n_i d_i \quad (5)$$

$$\Delta H_f = \sum \mathrm{BE} + \sum \mathrm{GE} + \mathrm{SE} + \mathrm{POP} + \mathrm{TOR} + \mathrm{T/R} \quad (6)$$

Equations 2–4 represent the bonding component of the enthalpy of formation as a summation of group increments while eq 6 uses instead sums of bond increments (BE) plus group corrections (GE). The two methods are equivalent. There is no theoretical basis for the dissections of ΔH_f as is done in eqs 2–4 and 6; the justification is that these equations and their relatives are capable of reproducing ΔH_f values within experimental error.

Many compounds exist at 298 K as a mixture of conformers. n-Butane, for example, consists of roughly 60–70% anti conformer and 40–30% gauche conformers (based on estimates of gauche values ranging from 0.70 to 1.0 kcal/mol).[25,32-34] Equation 2 represents directly the experimental enthalpy of formation of the compound, that is, of the conformer mixture. In equations 3, 4, and 6, however, the SE value is to be computed for a single conformer, the global minimum. The purpose of the SM (statistical mechanical) term of eqs 3 and 4 and the POP (population) term of eq 6 is to represent the contribution of the ΔH_f of other conformers of slightly greater energy than that of the global minimum. This contribution is about 0.27 kcal/mol for butane, more for higher alkanes. SM values are relatively insensitive to the value assumed for the energy of the gauche interaction. Tables of SM values are available.[20-23]

In principle, eq 3 is identical to eq 2, but there are important differences due to the properties of force fields. The quantity $\sum n_i a_i$ + SM approximates $\sum n_i b_i$ for molecules that do not require a steric correction, butane, for example. However, most force fields are not calibrated to give a zero value of SE for butane or any other molecule. Hence, a customized set of a increments must be obtained for each force field, even for minor variants of a single force field. This is accomplished by the determination of SE values and SM values for an appropriate and usually fairly large representative set of compounds for which experimental values of ΔH_f and estimates of SM are both available. Substitution of a count of the methyl, methylene, etc. groups, along with ΔH_f and SM values, into eq 3 provides an overdetermined set of simultaneous equations that may be solved by statistical methods for best values of the a increments.

Formal Steric Enthalpy, FSE. SE values are frequently used as measures of steric properties of specific conformers of molecules,[1] and they are often referred to as "strain" energies. A difficulty with this definition of steric properties is that it is indeterminate; the value assigned to a given conformer is different for each force field.

Steric properties may instead be defined by normalizing SE values to a common basis, the "formal steric enthalpy" (FSE). FSE values are defined in terms of a set of standard reference molecules having assigned FSE values.[16,19,20] The basis for the name is that FSE may be regarded as a standardized measure of the steric component of the enthalpy of formation. The reason for choice of a new name instead of using the name "strain" is that FSE has a precisely defined meaning while "strain" has many different meanings.

An appropriate set of standards for alkanes consists of n-butane and n-octane, both having an assigned FSE of 0, 2-methylbutane with assigned FSE = 0.70, and 2,2-dimethylbutane with assigned FSE = 1.40.[19,20,34-36] The defining conformers are the global minima.

Experimental estimates of FSE values are based on eq 4.[20-23] The first step was to evaluate the c increments. This has been done, and c increments have been determined for several classes of compounds as described elsewhere.[16,19,20] Given the c increments, the experimental ΔH_f, and an appropriate estimate of SM, eq 4 may be used to compute experimental FSE values.[20-23]

If a force field has been calibrated to conform to eq 3, then it is possibly by use of eq 5 to calculate FSE values without calculating ΔH_f values. It can be seen that eq 5 is the difference between eqs 4 and 3 and that $d_i = c_i - a_i$. The d corrections for alkanes and cycloalkanes are readily derived from the calculated SE values and the assigned FSE values for the above four alkanes.

If a force field is to be modified, it requires less work to recalibrate a set of d corrections than to recalibrate the a increments. This is so since it takes only n molecules to define n d corrections (in terms of standard molecules) while errors in experimental ΔH_f values make it advisable to use a much larger set of compounds to derive the a increments.[20] A problem that often arises is lack of precise information as to the compounds used to derive the original a increments.

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It may be possible to define and compute provisional FSE values even if ΔH_f data are not available for all compounds needed to calculate *a* increments. Note that *c* increments have been defined once for all; should better ΔH_f values or better SM estimates become available it might be desirable to do a recalibration. The $\sum n_i c_i$ of eq 4 may be called the "formal bond enthalpy", FBE, or the "strain-free enthalpy of formation."[36]

"Strain" Estimates with MM2(85). The basis for defining "strain" and "strainless" does not seem to be documented. "Strainless" is defined differently in MM2 and in MM3; the "strainless" BE and GE increments in MM3[9] are different from those in MM2(85).[8] Differences between H_f increments and "strainless" increments are also different. Should it become necessary to make additions to the force fields or modifications, there is no documented way to derive the necessary new increments for calculating strain estimates that are directly comparable to those given by the original parameters.

Advantages of FSE Compared with SE and ΔH_f as Measures of Steric Properties. The most important advantage of FSE over SE is that steric properties are defined in terms of standard molecules rather than in terms of the adventitious properties of force fields. FSE values provide a stable and unambiguous definition of steric properties. *FSE values are independent of any method of calculation that is capable of providing accurate enthalpies of formation.* The corollary is that the divergence between calculated and experimental FSE values provides an unambiguous measure of the performance of a force field.

Equations 2 and 4 share the common property that the bond enthalpy term, $\sum n_i b_i$ or $\sum n_i c_i$, is defined independently of the steric term. This is not true of SE and the associated increments of eqs 3 or 6, SE as a varying admixture of the steric component of the enthalpy and the bond component.

Another alternative is to convert SE values to enthalpies of formation. As can be seen from eq 4, for any particular force field the differences between experimental and calculated FSE values are identical to differences between experimental and calculated ΔH_f values. However, calculation of ΔH_f with eq 3 or eq 6 uses increments, which for different force fields are derived from different sets of experimental enthalpy data. The result is that for different force fields the errors for the ΔH_f and for FSE values do not usually have the same distributions.

There are other considerations. The steric component is often a rather small fraction of the enthalpy of formation. Whether recognized explicitly or not, it is the FSE value (or some equivalent counterpart) that is the actual target of a molecular mechanics calculation, and comparison of experimental and calculated FSE values provides the correct measure of the performance of a force field in reproducing enthalpy data. And finally, two molecules such as butane and octane having the same FSE value may have widely different enthalpies, and these differences in bond enthalpy obscure the steric component.

Use of SE and FSE Values for Calculation of Differences and Double Differences of Enthalpies. Equations 3–6 define the relationships between SE and FSE values and ΔH_f values; they also implicitly define relationships between differences of ΔH_f values and double differences of ΔH_f values. Consider first the familiar use of molecular mechanics to estimate relative energies of conformers of a given molecule. Since the comparisons are among single conformers, the SM and POP terms are zero; these terms apply only in treating populations of conformers. The T/R term of eq 6 is always 2.40, a constant. It is not entirely clear what is to be done about the TOR term of eq 6, but in practice it is treated as being independent of conformer. In eqs 3 and 4 the sums of increments will be the same for any two conformers of a given molecule, as will the sums of increments in eq 6. Thus the equalities of eq 7 hold.

$$\Delta H_f 2 - \Delta H_f 1 = \mathrm{SE2} - \mathrm{SE1} = \mathrm{FSE2} - \mathrm{FSE1} \quad (7)$$

The representation of differences of SE values of conformers of a given molecule as measures of differences of enthalpies of the conformers is thus consistent with the representations of ΔH_f in eqs 2–6.

The use of differences may be generalized. In comparisons among individual conformers of any two molecules, the difference of SE (or of FSE) values will be a proper estimate of the difference of enthalpies providing that the sums of increments cancel. This would be true for comparing the enthalpy difference between *cis*-1,2-dimethylcyclohexane and *cis*-1,3-dimethylcyclohexane, for example.

This does not work for comparisons in general. It does not work, for example, in comparing the SE difference between *trans*-1,2-dimethylcyclohexane (2) and *trans*-1,2-diisopropylcyclohexane (1). Since the summations of increments do not cancel, the difference of SE values, ΔSE(21) = SE(2) − SE(1), does not provide a proper estimate of the difference of enthalpies, $\Delta H_f(21)$, or of any other well-defined property. The value obtained will differ from one force field to the next. It would be possible in this case to calculate a difference of enthalpies by use of the full expressions of eqs 3–6, but that information does not tell much about steric properties because the enthalpy difference includes a residual bond component along with the intended steric component.

In the above example ΔFSE(21) = FSE(2) − FSE(1) does provide a useful measure of the difference of steric properties. This is so because FSE values represent defined steric properties that are independent of any properly calibrated force field. If we make calculations with two different force fields, ff1 and ff2, then we may predict that ΔFSE(21,ff1) − ΔFSE(21,ff2) will be nearly zero, while ΔSE(21,ff1) − ΔSE(21,ff2) may have any value whatever, depending on how the force fields were calibrated. Although the difference of FSE values represents a valid estimate of the difference in steric properties, it does not in this example equal the difference of ΔH_f values since the *c* increments do not cancel. With some comparisons *c* increments may be available for the substituents and it may be possible to compute the enthalpy difference even though increments are not available for the individual compounds. An example might be diethylamine and dineopentylamine.

Another use of molecular mechanics is to correlate and to predict equilibrium constants and rate constants.[37–46]

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Consider, for example, the formation of two lactones from hydroxy acids. The double difference of SE values (or of FSE values) can serve as an estimate of the double difference of enthalpies, providing, of course, that the force field is applicable to the acids and lactones under study. This assumes that the double difference of SM values will usually cancel. Whether cancellation occurs with eq 6 is not so clear with respect to TOR values. In any event, if the auxiliary terms do not cancel, it may be possible to correct the SE double difference so as to properly represent the double difference of enthalpies. The lactone equilibria will also involve appreciably different entropy terms, and these will have to be estimated by other methods.[38,45-48]

$$\text{HO–R1–COOH} \rightarrow \text{R1–OCO (lactone 1)}$$

$$\text{HO–R2–COOH} \rightarrow \text{R2–OCO (lactone 2)}$$

Incidentally, it has been shown that double differences of SE values of gaseous molecules can legitimately be used in linear free energy expressions for calculating reaction rates and equilibria *in solution*. This depends on the proposition that solvation effects to a first approximation tend to parallel steric effects as represented by ΔSE (or ΔFSE) values.[19]

Importance of Using an Invariant Force Field. Differences of SE values may be equated to differences of ΔH_f values only if the increments of eqs 3, 4, and 6 cancel exactly, and this absolute requirement will be met only if the identical force field is used for all calculations.

There are some MM2 and MM3 calculations for which the above requirement is not met, particularly the π calculations and calculations that activate the anomeric corrections. For these classes certain reference bond lengths and certain force constants are modified "on the fly." The force field is not a constant one even for different conformers of the same molecule. For such calculations neither the difference of SE values nor the difference of the ΔH_f values provide valid measures of the desired differences of enthalpies.

Procedures for Calculation of FSE Values with the MM2 and MM3 Force Fields. Examination of the several representations of ΔH_f, eqs 3, 4, and 6, shows that eq 6 has two extra terms, TOR and T/R. A force field calibrated to use eq 6 cannot be expected to conform entirely to eqs 3 and 4 for compounds having different TOR components.

What is the theoretical significance of T/R? The intent of including the T/R term is clear; it assumes that SE values pertain to 0 K and that ΔH_f values should also pertain to 0 K unless or until converted to 298 K. Parenthetically it may be remarked that it has never been demonstrated that a force can be constructed that gives correct values at 0 K but incorrect values at 298 K. Bond or group increments of eqs 3, 4, and 6 are conventionally based on enthalpy data at 298 K. The choices for calibrating the increments are two; in eqs 3 and 4 the increments are calibrated to include all corrections appropriate for 298 K. In eq 6 the T/R term is first subtracted out before calculating the increments so that they are applicable to 0 K, and then T/R is added back to reconvert to 298 K. It is not apparent that these extra steps accomplish anything useful.

What is the significance of the TOR term? This is described as being a Pitzer type of correction.[1] No clear rationale has been offered for the need for such a term since all such components can be included in the increments. If the component represented by TOR has to be treated separately, then equally good arguments could be presented for dissecting out other bond enthalpy components for separate treatment. There is a practical difficulty with the TOR term in that selection of the proper value is often ambiguous; there are many compounds for which the proper choice has not been defined.

How may FSE values best be estimated with the MM2 and MM3 force fields? One possibility is to compute ΔH_f values with eq 6 and substitute these into eq 4, making use of published *c* increments and SM values. An alternative is to reverse this approach for cyclic compounds, for which TOR and POP are generally zero and for acyclic compounds to develop d-corrections for use in eq 5. This latter has been adopted in this study. It has the advantage of avoiding the considerable ambiguities in choices of POP and TOR values almost entirely. There is no published documentation about POP values. To some extent they can be estimated by back calculations of reported enthalpy and "strain" data, and this is the source of the POP values I have used.

Calculation of *d* Corrections for MM2. All calculations in this study are based on the MM2(85) force field and were carried out with the MM2(85) program. The MM2(77),[49] MM2(85),[8] and MM2(87)[50] force fields are alike for the types of compounds treated in this study. MM2(85) differs from MM2(77) in addition of new types of atoms and additional terms for these. MM2(87) adds a new method for treating hydrogen bonding and several further terms.

It is important to remark that the MM2 and MM3 programs perform force field modifications "on-the-fly" with the consequence that the printed force field does not exactly correspond to the one used for certain classes of compounds. Different results will be obtained with a non-MM2 program unless it too makes such changes. The output always reports the values actually used in the calculation. Careful consideration was given to such changes. The only one that concerns the calculations reported in this study is the electronegativity corrections used for the oxygen-containing compounds. Although the bond reference distances actually used for C–O bonds, for example, differ slightly from those printed out in the general force field summary, the effective values are consistent within families and may simply be considered to be extensions of the standard force field.

The standard compounds used to define FSE values are those published.[20-23] SE values were obtained for the global minimum conformer of each standard compound. These, together with the assigned FSE values, were substituted in eq 5 to provide sets of simultaneous equations that were solved for d-corrections. Results are summarized in Table I.

For classes other than alkanes the equations defining *d* corrections are underdetermined and it is necessary to make one arbitrary assignment. I have chosen to set *d*[C_C_CDH_H_] = *d*[C_C_C_H_H_].[21] Likewise the *d*[C_C_H_H_O_] value, the *d*[C_C_CEH_H_] value, and the *d*[C_C_CKH_H_] value have also been assigned equal to the *d*[C_C_C_H_H_] value.[22,23]

Results with Alkanes. Table II (Supplementary material) summarizes the calculation of ΔH_f values for a

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Table I. *d* Corrections for Alkanes, Olefins, Alcohols, Ethers, Aldehydes, Ketones, Acids, and Esters for the MM2(85) Force Field

structural[a] element	ref compd	SE[b]	FSE assigned	*d* corrctn[c]
d[C_C_H_H_H_]	(butane)	2.17	0.00	0.443
d[C_C_C_H_H_]	(octane)	4.74	0.00	0.643
d[C_C_C_C_H_]	2-methylbutane	3.63	0.70	0.959
d[C_C_C_C_C_]	2,2-dimethylbutane	5.01	1.40	1.196
d[CDCDH_H_]	1-butene	1.48	0.00	0.232
d[CDC_CDH_]	(*E*)-3-hexene	5.16	0.00	0.166
d[CDC_C_CD]	2-methylpropene	−0.04	0.00	−0.066
d[C_CDH_H_H_]	(*E*)-2-butene	0.13	0.00	−0.100
d[C_C_CDH_H_]				(0.643)
d[C_C_C_CDH_]	3-methyl-1-butene	2.47	0.00	1.190
d[C_C_C_C_CD]	3,3-dimethyl-1-butene	3.29	0.40	1.161
d[C_CDCDH_H_]	1,4-pentadiene	2.00	0.00	1.200
d[C_C_CDCDH_]	3-methyl-1,4-pentadiene	3.63	0.00	2.388
d[C_C_C_CDCD]	3,3-dimethyl-1,4-pentadiene	5.98	0.80	3.501
d[O_C_H_]	1-propanol	2.384	0.00	0.655
d[O_C_C_]	diethyl ether	5.816	0.00	3.645
d[C_H_H_H_O_]	ethyl methyl ether	5.269	0.00	0.538
d[C_C_H_H_O_]				(0.643)
d[C_C_C_H_O_]	2-butanol	3.772	0.20	1.388
d[C_C_C_C_O_]	2-methyl-2-butanol	5.806	0.90	2.280
d[CKC_H_OK]	propanal	0.89	0.00	−0.194
d[CKC_C_OK]	3-pentanone	1.05	0.00	−1.118
d[C_CKH_H_H_]	2-butanone	0.29	0.00	0.321
d[C_C_CKH_H_]				(0.643)
d[C_C_C_CKH_]	3-methyl-2-butanone	2.23	0.00	2.145
d[C_C_C_C_CK]	3,3-dimethyl-2-butanone	4.64	0.00	4.111
d[CEC_OEOH]	propanoic acid	−3.039	0.00	−4.125
d[CEC_OCOE]	methyl propanoate	5.719	0.85	3.244
d[C_CEH_H_H_]	methyl acetate	5.004	0.85	0.371
d[C_C_CEH_H_]				(0.643)
d[C_C_C_CEH_]	methyl 2-methylpropanoate	7.222	0.85	1.703
d[C_C_C_C_CE]	methyl 2,2-dimethylpropanoate	8.946	0.85	2.984

[a] The first symbol represents the main atom. The remaining symbols represent the ligands. C_ is sp^3 carbon, CD is sp^2 carbon of an olefin, CE is sp^2 carbon of an ester or an acid, CK is sp^2 carbon of an aldehyde or a ketone, H_ is hydrogen attached to carbon, O_ is sp^3 oxygen, OC denotes the alkoxyl oxygen of esters attached to sp^3 carbon, OE denotes the sp^2 oxygen of esters and acids, OH denotes the carboxylic OH group, and OK denotes the sp^2 oxygen of aldehydes and ketones. [b] MM2(85) value. [c] Values in parentheses are defined values.

representative set of alkanes based on eq 4, using FSE values calculated by eq 5. As expected, the resultant ΔH_f values fall into two groups. For acyclic alkanes the calculated ΔH_f values are reasonable. However, values for the cyclic alkanes are too positive by from 1 to 4 kcal/mol. (The relevant data are repeated in Tables III and IV below.)

The reason for the discrepancy has been discussed above and is due to the presence of the TOR term in eq 6 and also to POP values that are too large.

The calculation of ΔH_f of acyclic alkanes with eq 6 requires assignment of appropriate POP and TOR terms; for many cyclic molecules these terms are zero. Table II (supplementary material) includes POP and TOR assignments, and the resultant ΔH_f values calculated with eq 6. There are uncertainties about correct assignments of POP since this feature does not seem to have been documented. For a few compounds there are also ambiguities as to the correct value for TOR. Back calculations suggest that an increment of 0.30–0.35 kcal/mol per methylene unit has been used for POP; the correct increment is instead about 0.21. Best ΔH_f values for use in eq 6 with this particular set of alkanes are obtained with an increment of about 0.30.

It was important to establish that the values adopted for POP and TOR are in accord with those used to obtain published ΔH_f values. That the choices are appropriate may be seen by comparison of the ΔH_f data in Table II (calculated with eq 6) with corresponding data in Table 5.1 of ref 1. Twenty-five of the compounds appear in both tables. The calculated ΔH_f values in column 9, based on eq 6, agree within 0.05 kcal/mol for 18. Exceptions include 2,3-dimethylbutane −0.28, 2,2,3-trimethylbutane −0.37, heptane +0.40, and 3,3-diethylpentane −1.92.

Table III summarizes the calculation of FSE values by eq 5 and of ΔH_f values by eq 4 for acyclic alkanes based on SE values calculated with MM2(85). It should be noted that the calculations summarized in Table III make no use of POP, TOR, or of the T/R term. Agreement between calculated and experimental FSE values (or equivalently between calculated and experimental ΔH_f values) has a standard deviation of 1.16 kcal/mol. The corresponding agreement between observed and calculated ΔH_f values for the same acyclic alkanes based on eq 6 is 1.10. That is, eqs 4 and 6 are equally applicable to these data. The reasons for the relatively large errors are not known.

The conclusion is that correct FSE values and correct ΔH_f values can be obtained with the MM2(85) force field for acyclic alkanes either by use of eq 6 or by use of eqs 4 and 5. As anticipated above from the analysis of eq 6, it is not necessary to include TOR values or unusually large POP values (or to use the T/R term) to obtain correct FSE and ΔH_f values with the MM2(85) force field. In other words it is possible to derive appropriate sets of increments for either eqs 4 and 5 or for eq 6 for acyclic molecules.

FSE values for cyclic alkanes must be calculated indirectly, and this has been done in Table IV. The default ΔH_f value reported by the MM2(85) program is based on POP and TOR, both zero. This value can be used as the "observed" ΔH_f value in eq 4; SM is zero for the compounds in Table IV except for methylcyclohexane. FSE is the difference between the MM2 ΔH_f value and the $\sum n_i c_i$ term. The standard deviation of the difference between experimental and calculated FSE values is 0.57 kcal/mol for this set of cyclic alkanes.

Results with Other Classes of Compounds. Table V reports results for olefins, Table VI for alcohols and ethers, Table VII (Supplementary Material) for aldehydes and ketones, and Table VIII (Supplementary Material) for acids and esters. The problems of deciding correct POP and TOR values for these compounds are numerous, since there seem to be no published guidelines. The values I have selected are reported in the tables.

For the 34 olefins in Table V, including 4 cyclic olefins, the differences between observed and calculated ΔH_f values show a standard deviation of 1.4 based on eq 6 and 1.3 based on eq 4. Omitting values for the four cyclic olefins did not change the standard deviations.

Experimental enthalpy of formation data for alcohols and ethers are fairly extensive, but the quality of some is questionable. As reported elsewhere, *the data for the*

Table III. Formal Steric Enthalpies Based on MM2(85) SE Values and Derived Enthalpies of Formation of Acyclic Alkanes Based on Eqs 4 and 5

compd		FSE[a] exptl	FSE[b] calcd	FBE[c]	SM[d]	ΔH_f[e] calcd from FBE, FSE	ΔH_f[f] exptl avg	diff[g]	SE[h]	H_f0[i]
2-methylpropane	C_4H_{10}	0.25	−0.34	−32.36	0.00	−32.70	−32.11	0.59	1.94	−32.17
butane	C_4H_{10}	0.01	0.00	−30.36	0.27	−30.09	−30.09	0.00	2.17	−30.51
2,2-dimethylpropane	C_5H_{12}	0.43	−0.70	−40.35	0.00	−41.05	−39.93	1.12	2.27	−40.55
2-methylbutane	C_5H_{12}	0.58	0.70	−37.50	0.09	−36.71	−36.83	−0.12	3.63	−36.90
pentane	C_5H_{12}	−0.02	0.01	−35.51	0.47	−35.03	−35.06	−0.03	2.82	−36.27
2,2-dimethylbutane	C_6H_{14}	1.09	1.40	−45.50	0.00	−44.10	−44.42	−0.32	5.01	−44.22
2,3-dimethylbutane	C_6H_{14}	2.10	2.12	−44.65	0.00	−42.53	−42.55	−0.02	5.80	−42.57
2-methylpentane	C_6H_{14}	0.68	0.76	−42.65	0.25	−41.64	−41.72	−0.08	4.33	−42.62
3-methylpentane	C_6H_{14}	1.45	1.96	−42.65	0.13	−40.56	−41.08	−0.52	5.53	−41.41
hexane	C_6H_{14}	0.01	0.01	−40.65	0.69	−39.95	−39.95	−0.00	3.47	−42.05
2,2,3-trimethylbutane	C_7H_{16}	3.73	3.90	−52.64	0.00	−48.74	−48.92	−0.18	8.27	−48.81
2,2-dimethylpentane	C_7H_{16}	1.34	1.44	−50.64	0.06	−49.14	−49.24	−0.10	5.70	−49.95
2,4-dimethylpentane	C_7H_{16}	1.43	1.29	−49.80	0.13	−48.38	−48.25	0.13	5.62	−49.17
3,3-dimethylpentane	C_7H_{16}	2.49	3.98	−50.64	0.02	−46.64	−48.13	−1.49	8.24	−47.71
3-ethylpentane	C_7H_{16}	1.97	3.52	−47.80	0.51	−43.77	−45.33	−1.56	7.73	−45.63
heptane	C_7H_{16}	0.02	0.01	−45.80	0.91	−44.88	−44.87	0.01	4.11	−47.82
2,2,3,3-tetramethylbutane	C_8H_{18}	6.68	6.74	−60.63	0.00	−53.89	−53.96	−0.07	11.79	−54.00
2,2,3-trimethylpentane	C_8H_{18}	5.10	7.46	−57.79	0.10	−50.23	−52.60	−2.37	12.47	−51.03
2,2,4-trimethylpentane	C_8H_{18}	4.22	4.23	−57.79	0.02	−53.54	−53.56	−0.02	9.24	−54.26
2,3,3-trimethylpentane	C_8H_{18}	5.98	6.74	−57.79	0.10	−50.95	−51.72	−0.77	11.75	−51.74
3,3-dimethylhexane	C_8H_{18}	3.12	4.05	−55.79	0.08	−51.66	−52.60	−0.94	8.95	−53.11
octane	C_8H_{18}	−0.01	0.00	−50.95	1.12	−49.83	−49.84	−0.01	4.74	−53.60
2,2,3,3-tetramethylpentane	C_9H_{20}	8.96	11.00	−65.78	0.14	−54.64	−56.69	−2.05	16.70	−55.50
2,2,3,4-tetramethylpentane	C_9H_{20}	8.11	8.05	−64.93	0.19	−56.69	−56.63	0.06	13.82	−57.52
2,2,4,4-tetramethylpentane	C_9H_{20}	8.00	7.09	−65.78	0.00	−58.69	−57.79	0.90	12.79	−59.41
3,3-diethylpentane	C_9H_{20}		7.89	−60.94			−55.48		13.44	−55.05
decane	$C_{10}H_{22}$	0.04	−0.01	−61.24	1.55	−59.70	−59.65	0.05	6.02	−65.15
2,2,4,4,5-pentamethylhexane	$C_{11}H_{24}$	10.85	13.01	−78.07	0.06	−65.00	−67.16	−2.16	20.11	−66.36
3,3,5,5-tetramethylheptane	$C_{11}H_{24}$	9.90	13.17	−76.07	0.04	−62.86	−66.13	−3.27	20.16	−64.88
tri-*tert*-butylmethane	$C_{13}H_{28}$	36.81	38.07	−93.21	0.00	−55.14	−56.40	−1.26	46.61	−56.41
sym-tetra-*tert*-butylethane	$C_{18}H_{38}$*	65.88	59.78	−125.78	0.00	−66.00	−59.90	6.10	71.81	−68.44

[a] Reference 20. [b] From equation 5. [c] FBE is the sum of n_ic_i using the c increments of ref 20. [d] From ref 20. [e] Using eq 4; FBE from column 5, FSE calcd from column 4, SM from column 6. [f] From ref 20. [g] Diff is the entry in column 8 minus the entry in column 7. [h] SE from the MM2(85) calculation. [i] H_f0 reported by the MM2(85) program if POP and TOR are zero (the default). * Omitted from estimation of standard deviation of FSE(exptl) − FSE(calc).

Table IV. Formal Steric Enthalpies of Cycloalkanes from H_f0 Values Calculated with MM2(85)

compd		FSE[a] exptl	FSE[b] calcd from SE	FSE[c] calcd from H_f0–FBE	FBE[d]	SM[e]	ΔH_f[f] exptl avg	H_f0[g]	diff[h]	SE[i]
cyclohexane	C_6H_{12}	1.42	2.69	1.35	−30.88	0.00	−29.46	−29.53	0.07	6.55
bicyclo[2.2.1]heptane	C_7H_{12}	17.13	17.97	17.41	−30.25	0.00	−13.12	−12.84	−0.28	23.09
methylcyclohexane	C_7H_{14}	0.98	2.28	0.99	−38.03	0.07	−36.98	−37.04	0.06	6.89
bicyclo[2.2.2]octane	C_8H_{14}	11.74	13.87	12.69	−35.40	0.00	−23.66	−22.71	−0.95	19.64
cis-1,2-dimethylcyclohexane	C_8H_{16}	2.77	3.97	2.65	−46.02	0.00	−43.25	−43.37	0.12	9.27
trans-1,2-dimethylcyclohexane	C_8H_{16}	2.16	3.09	1.86	−45.17	0.00	−43.01	−43.31	0.30	8.46
cis-1,3-dimethylcyclohexane	C_8H_{16}	1.03	1.84	0.60	−45.17	0.00	−44.14	−44.57	0.43	7.21
trans-1,3-dimethylcyclohexane	C_8H_{16}	2.98	3.65	2.41	−45.17	0.00	−42.19	−42.76	0.57	9.02
cis-1,4-dimethylcyclohexane	C_8H_{16}	2.96	3.60	2.36	−45.17	0.00	−42.22	−42.81	0.59	8.97
trans-1,4-dimethylcyclohexane	C_8H_{16}	1.06	1.85	0.61	−45.17	0.00	−44.11	−44.56	0.45	7.22
adamantane	$C_{10}H_{16}$	7.74	9.39	8.37	−39.91	0.00	−32.17	−31.54	−0.63	17.07
bicyclo[4.4.0]decane (*cis*-decalin)	$C_{10}H_{18}$	5.25	7.09	4.66	−45.69	0.00	−40.44	−41.03	0.59	14.15
bicyclo[4.4.0]decane (*trans*-decalin)	$C_{10}H_{18}$	2.17	4.36	1.93	−45.69	0.00	−43.52	−43.76	0.24	11.42
1,3,5,7-tetramethyladamantane	$C_{14}H_{24}$	4.15	9.56	5.42	−71.88	0.00	−67.73	−66.46	−1.27	19.99
trans,anti,trans-tetradecahydroanthracene	$C_{14}H_{24}$	7.78	12.01	8.50	−60.50	0.00	−52.72	−52.00	−0.72	22.27
trans,syn,trans-tetradecahydroanthracene	$C_{14}H_{24}$	2.37	5.91	2.40	−60.50	0.00	−58.13	−58.10	−0.03	16.17

[a] Reference 20. [b] From eq 5. [c] Column 9 minus column 6 minus column 7. [d] FBE is the sum of n_ic_i using the c increments of ref 20. [d] From ref 20. [e] From ref 20. [f] From ref 20. [g] H_f0 reported by the MM2(85) program if POP and TOR are zero (the default). [h] Diff is the entry in column 8 minus the entry in column 9. [h] SE from the MM2(85) calculation.

cyclohexanols are suspect.[22] There are also some serious discrepancies between the Stull compilation[51] and the Pedley, Naylor, and Kirby compilations.[26,28,52] Examples are 1-pentanol, methyl *tert*-butyl ether, 1-hexanol, 1-no-

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(51) Stull, D. R.; Westrum, E. F., Jr.; Sinke, G. C. *The Chemical Thermodynamics of Organic Compounds*; John Wiley & Sons: New York, 1969.

(52) Pedley, J. B.; Rylance, J. *Sussex-N.P.L. Computer Analysed Thermochemical Data Organic and Organometallic Compounds*; University of Sussex: Sussex, UK, 1977.

Table V. Calculated Enthalpies of Formation and Formal Steric Enthalpies of Olefins

compound		FSE[a] exptl	FSE[b] calcd	FBE[c]	SM[d]	ΔH_f[e] calcd from FBE, FSE	ΔH_f[f] exptl avg	ΔH_f[g] H_f0 + POP + TOR	Diff[h]	SE[i]	H_f0[j]	TOR[k]	POP[l]
ethylene	C_2H_4	−0.11	−0.04	12.63	0.00	12.59	12.53	12.84	−0.31	0.42	12.84	0	0.0
propene	C_3H_6	−0.09	−0.06	4.92	0.00	4.86	4.83	4.91	−0.08	0.24	4.91	0	0.0
1-butene	C_4H_8	0.14	0.00	−0.23	0.09	−0.14	−0.01	0.11	−0.12	1.48	−0.26	1	0.0
(*E*)-2-butene	C_4H_8	0.10	0.00	−2.79	0.00	−2.79	−2.70	−2.95	0.25	0.13	−2.95	0	0.0
(*Z*)-2-butene	C_4H_8	1.11	1.43	−2.79	0.00	−1.36	−1.69	−1.52	−0.17	1.56	−1.52	0	0.0
2-methylpropene	C_4H_8	−0.43	−0.00	−3.61	0.00	−3.61	−4.04	−4.40	0.36	−0.03	−4.40	0	0.0
1,4-pentadiene	C_5H_8	0.00	0.00	25.04	0.18	25.22	25.22	25.52	−0.30	2.00	24.78	2	0.0
1-pentene	C_5H_{10}	−0.04	0.02	−5.37	−.36	−5.00	−5.05	−4.98	−0.07	2.14	−6.02	2	1.0
2-methyl-1-butene	C_5H_{10}	0.11	0.69	−8.76	0.09	−7.99	−8.56	−8.57	0.01	1.84	−8.94	1	0.0
2-methyl-2-butene	C_5H_{10}	1.24	1.93	−11.32	0.00	−9.40	−10.08	−10.39	0.31	1.72	−10.39	0	0.0
(*E*)-2-pentene	C_5H_{10}	0.24	0.02	−7.93	0.09	−7.82	−7.61	−7.79	0.18	1.34	−8.16	1	0.0
(*Z*)-2-pentene	C_5H_{10}	1.19	1.30	−7.93	0.09	−6.54	−6.66	−6.51	−0.15	2.62	−6.88	1	0.0
3-methyl-1-butene	C_5H_{10}	0.56	0.00	−7.37	0.05	−7.32	−6.76	−6.75	−0.01	2.47	−7.12	1	0.0
1,5-hexadiene	C_6H_{10}	−0.01	2.79	19.61	0.50	22.90	20.10	22.95	−2.85	4.87	21.24	3	2.0
cyclohexene	C_6H_{10}	2.07	1.28	−3.31	0.00	−2.03	−1.24	−2.29	1.05	4.19	−2.29	0	0.0
2,3-dimethyl-1-butene	C_6H_{12}	0.94	1.57	−15.90	0.00	−14.33	−14.96	−14.54	−0.42	3.71	−14.91	1	0.0
2,3-dimethyl-2-butene	C_6H_{12}	3.55	5.20	−19.85	0.00	−14.65	−16.30	−16.47	0.17	4.67	−16.47	0	0.0
(*E*)-2-hexene	C_6H_{12}	−0.10	0.03	−13.08	0.30	−12.75	−12.88	−12.88	0.00	1.99	−13.92	2	1.0
(*Z*)-2-hexene	C_6H_{12}	0.28	1.25	−13.08	0.30	−11.53	−12.51	−11.66	−0.85	3.21	−12.70	2	1.0
3,3-dimethyl-1-butene	C_6H_{12}	0.90	0.40	−15.36	0.00	−14.96	−14.46	−14.64	0.18	3.29	−15.01	1	0.0
(*E*)-3-hexene	C_6H_{12}	−0.11	0.00	−13.08	0.18	−12.90	−13.01	−12.66	−0.35	2.50	−13.40	2	0.0
(*Z*)-3-hexene	C_6H_{12}	1.52	1.10	−13.08	0.18	−11.80	−11.38	−11.57	0.19	3.60	−12.31	2	0.0
3-methyl-1-pentene	C_6H_{12}	0.39	0.96	−12.52	0.30	−11.26	−11.83	−11.16	−0.67	4.08	−11.90	2	0.0
4-methyl-1-pentene	C_6H_{12}	0.08	0.58	−12.52	0.18	−11.76	−12.26	−11.80	−0.46	3.47	−12.54	2	0.0
4,4-dimethyl-1-pentene	C_7H_{14}	0.92	0.65	−20.51	0.09	−19.78	−19.50	−19.76	0.26	4.22	−20.50	2	0.0
(*E*)-4,4-dimethyl-2-pentene	C_7H_{14}	1.85	0.36	−23.07	0.00	−22.71	−21.22	−22.60	1.38	3.08	−22.97	1	0.0
(*Z*)-4,4-dimethyl-2-pentene	C_7H_{14}	5.72	3.24	−23.07	0.00	−19.83	−17.35	−19.72	2.37	5.96	−20.09	1	0.0
2-bicyclo[2.2.2]octene	C_8H_{12}	12.72	13.46	−7.82	0.00	5.64	4.90	5.53	−0.63	18.28	5.53	0	0.0
(*E*)-2,2-dimethyl-3-hexene	C_8H_{16}	2.39	0.27	−28.22	0.09]	−27.86	−25.74	−27.55	1.81	4.18	−28.29	2	0.0
(*Z*)-2,2-dimethyl-3-hexene	C_8H_{16}	6.79	3.02	−28.22	0.09	−25.11	−21.34	−24.79	3.45	6.93	−25.53	2	0.0
2,4,4-trimethyl-1-pentene	C_8H_{16}	2.61	2.42	−29.04	0.00	−26.62	−26.43	−27.34	0.91	5.66	−28.08	2	0.0
2,4,4-trimethyl-2-pentene	C_8H_{16}	6.53	3.88	−31.60	0.00	−27.72	−25.07	−28.44	3.37	6.26	−28.81	1	0.0
2-methylbicyclo-[2.2.2]oct-2-ene	C_9H_{14}	11.91	13.48	−16.36	0.00	−2.88	−4.45	−3.27	−1.18	18.51	−3.27	0	0.0
2-methylenebicyclo-[2.2.2]octane	C_9H_{14}	11.60	13.56	−13.80	0.00	−0.24	−2.20	−1.59	−0.61	18.86	−1.59	0	0.0

[a] Reference 21. [b] From eq 5. [c] FBE is the sum of n_ic_i using the *c* increments of ref 21. [d] From ref 21. [e] Using eq 4; FBE from column 5, FSE calculated from column 4, SM from column 6. Standard deviation of observed − calculated ΔH_f is 1.3 kcal/mol for 34 olefins. [f] From ref 21. [g] Equation 6. H_f0 is default value; TOR is 0.36 times the entry in column 13, POP is 0.30 times the entry in column 14. [h] Diff is the entry in column 8 minus the entry in column 9. The standard deviation based on eq 6 is 1.4 kcal/mol. [i] SE from the MM2(85) calculation. [j] H_f0 reported by the MM2(85) program if POP and TOR are zero (the default). [k] The number of bonds for the Pitzer "correction." [l] See text.

nanol, and 1-decanol. Representative calculated values are given in the Pedley, Naylor, and Kirby compilations.[26,28,52] Examples are 1-pentanol, methyl *tert*-butyl ether, 1-hexanol, 1-nonanol, and 1-decanol. Representative calculated values are given in Table VI. In analyzing the results, the data for the compounds marked with an asterisk have been omitted from estimates of standard deviations on the grounds that they appear to be in serious error. All alcohols and ethers included in the error estimates are acyclic except for cyclohexanol. All oxygen atoms had two lone pairs as required by the MM2 force field. The standard deviation for observed minus calculated ΔH_f for 25 compounds is 1.05 with eq 6 and 0.57 with eq 4.

There are relatively few experimental data for aldehydes and ketones and for esters. The data in supplementary Table VIII are based on esters and acids having two lone pairs on the alkoxyl oxygen and none on the carbonyl oxygen. Lone pairs are not used on the carbonyl oxygens with the MM2 family of force fields.

To summarize: application of eqs 4 and 5 gives as good, or better, ΔH_f values than does eq 6 for the acyclic compounds. This demonstrates that the MM2 force field does not require T/R, TOR, and the overly large POP values in order to reproduce experimental ΔH_f values. It appears that MM2(85) is not well calibrated for highly crowded molecules. Results obtained with other force fields are better for acyclic alkanes and comparable for the other classes of compounds treated here.[16-18]

Calculations

Much of the work was carried out with an overlaid version of MM2(85) on a PC-XT. Minor modifications were necessary to provide for specification of I/O files and to replace time and date routines; these facilities are system specific. The PC-XT version also had the dimensioning reduced to 100 atoms. There were no changes to the program logic or to any of the internal data. Some calculations utilized an archival version of the MM2(85) force field as deposited with QCPE with the program FFMAIN. For this version the K-subroutines were modified to read an external force

Table VI. Calculated Enthalpies of Formation and Formal Steric Enthalpies of Alcohols and Ethers

compd		FSE[a] exptl	FSE[b] calcd	FBE[c]	SM[d]	ΔH_f[e] calcd from FBE, FSE	ΔH_f[f] exptl avg	ΔH_f[g] H_f0 + POP + TOR	diff[h]	SE[i]	H_f0[j]	TOR[k]	POP[l]
methanol	C_1H_4O	−0.53	−0.06	−47.59	0.00	−47.66	−48.12	−47.57	−0.55	1.13	−47.57	0	0.0
ethanol	C_2H_6O	−0.22	−0.03	−55.95	0.00	−55.98	−56.17	−55.81	−0.36	1.71	−55.81	0	0.0
1-propanol	C_3H_8O	−0.29	0.00	−61.10	0.12	−60.98	−61.27	−61.26	−0.01	2.38	−61.56	0	1.0
2-propanol	C_3H_8O	0.03	−0.24	−65.18	0.00	−65.42	−65.15	−65.12	−0.03	2.69	−65.12	0	0.0
ethyl methyl ether	C_3H_8O	0.28	0.00	−52.25	0.25	−52.00	−51.73	−51.24	−0.49	5.27	−51.91	1	1.0
1-butanol	$C_4H_{10}O$	0.25	0.02	−66.24	0.33	−65.89	−65.66	−66.34	0.68	3.04	−67.31	1	2.0
2-butanol	$C_4H_{10}O$	0.14	0.20	−70.32	0.25	−69.87	−69.93	−69.78	−0.15	3.77	−70.45	1	1.0
2-methyl-1-propanol	$C_4H_{10}O$	0.42	0.05	−68.24	0.05	−68.14	−67.77	−68.93	1.16	3.19	−68.93	0	0.0
2-methyl-2-propanol	$C_4H_{10}O$	0.06	0.28	−74.74	0.00	−74.46	−74.68	−73.66	−1.02	4.54	−73.66	0	0.0
diethyl ether	$C_4H_{10}O$	−0.13	0.00	−60.61	0.47	−60.14	−60.27	−58.86	−1.41	5.82	−60.20	2	2.0
methyl isopropyl ether	$C_4H_{10}O$	1.17	1.10	−61.48	0.08	−60.30	−60.24	−59.23	−1.01	7.56	−59.90	1	1.0
methyl *n*-propyl ether	$C_4H_{10}O$	−0.16	0.00	−57.40	0.68	−56.72	−56.88	−56.35	−0.53	5.91	−57.69	2	2.0
1-pentanol	$C_5H_{12}O$	−0.51	0.02	−71.39	0.53	−70.84	−71.37	−71.44	0.07	3.69	−73.08	2	3.0
2-methyl-1-butanol	$C_5H_{12}O$	1.00	1.18	−73.39	0.15	−72.06	−72.24	−72.27	0.03	4.96	−73.24	1	2.0
2-methyl-2-butanol	$C_5H_{12}O$	0.96	0.90	−79.89	0.09	−78.90	−78.84	−78.44	−0.40	5.81	−78.81	1	0.0
2-pentanol	$C_5H_{12}O$	0.14	0.21	−75.47	0.46	−74.80	−74.87	−74.87	0.00	4.43	−76.21	2	2.0
3-methyl-2-butanol	$C_5H_{12}O$	2.17	1.20	−77.47	0.09	−76.18	−75.22	−75.86	0.64	5.53	−76.53	1	1.0
3-pentanol	$C_5H_{12}O$	−0.67	0.61	−75.47	0.38	−74.48	−75.76	−74.46	−1.30	4.83	−75.80	2	2.0
ethyl *n*-propyl ether	$C_5H_{12}O$	0.01	−0.01	−65.76	0.69	−65.08	−65.06	−63.97	−1.09	6.45	−65.98	3	3.0
methyl *tert*-butyl ether	$C_5H_{12}O$	2.16	2.26	−71.04	0.00	−68.78	−68.88	−67.14	−1.74	10.06	−67.81	1	1.0
cyclohexanol	$C_6H_{12}O$	1.45	2.44	−70.85	0.00	−68.41	−69.40	−69.92	0.52	7.70	−69.92	0	0.0
diisopropyl ether	$C_6H_{14}O$	2.71	2.21	−79.06	0.11	−76.74	−76.25	−74.83	−1.42	10.40	−76.17	2	2.0
cis-2-methylcyclohexanol	$C_7H_{14}O$*[m]	−0.16	3.07	−77.99	0.00	−74.92	−78.15	−76.38	−1.77	9.08	−76.38	0	0.0
trans-2-methylcyclohexanol	$C_7H_{14}O$*	−6.26	2.42	−77.99	0.00	−75.57	−84.25	−77.03	−7.22	8.43	−77.03	0	0.0
cis-3-methylcyclohexanol	$C_7H_{14}O$*	−5.88	2.00	−77.99	0.00	−75.99	−83.87	−77.45	−6.42	8.02	−77.45	0	0.0
trans-3-methylcyclohexanol	$C_7H_{14}O$*	−0.67	2.61	−77.99	0.00	−75.38	−78.66	−76.84	−1.82	8.62	−76.84	0	0.0
cis-4-methylcyclohexanol	$C_7H_{14}O$*	−5.06	2.49	−77.99	0.00	−75.50	−83.05	−76.86	−6.19	8.50	−76.86	0	0.0
trans-4-methylcyclohexanol	$C_7H_{14}O$*	−9.77	2.01	−77.99	0.00	−75.98	−87.76	−77.44	−10.3	8.02	−77.44	0	0.0
isopropyl *tert*-butyl ether	$C_7H_{16}O$	3.10	4.00	−88.63	0.00	−84.63	−85.54	−82.47	−3.07	13.53	−83.44	1	2.0
di-*n*-butyl ether	$C_8H_{18}O$	0.13	−0.02	−81.20	1.33	−79.89	−79.74	−79.29	−0.45	8.37	−83.31	6	6.0
di-*tert*-butyl ether	$C_8H_{18}O$	11.33	9.85	−98.19	0.00	−88.34	−86.86	−85.69	−1.17	20.71	−86.66	1	2.0

[a] Reference 22. [b] From eq 5. [c] FBE is the sum of n_ic_i using the c increments of ref 20. [d] From ref 22. [e] Using eq 4; FBE from column 5, FSE calculated from column 4, SM from column 6. Standard deviation for 25 alcohols and ethers (omitting those marked with an asterisk) is 0.57. [f] From ref 22. [g] Equation 6. H_f0 is default value; TOR is 0.36 times the entry in column 13, POP is 0.30 times the entry in column 14. [h] Diff is the entry in column 8 minus the entry in column 9. See also Table V. Standard deviation for 25 alcohols and ethers is 1.05 kcal/mol (omitting the compounds marked with an asterisk). [i] SE from the MM2(85) calculation. [j] H_f0 reported by the MM2(85) program with TOR and POP both zero (default). [k] The number of bonds for the Pitzer "correction". See text. [l] See text. [m] ΔH_f values of compounds labeled with an asterisk are considered to be uncertain and are not included in the statistics.

field derived from the MM2(85) force field in FFMAIN format.[53] Some runs were made with the full version of MM2(85). Extensive test runs showed that all versions gave identical results on all computers. Data were processed with dBASE(TM) or with spread sheet programs.

Part of the I/O modification was incorporation of ability to read the command tail so as to get the name of the input file. It was then possible to use the facilities of the MSDOS operating system to stack runs for automatic batch processing. A copy of the overlaid version has been submitted to QCPE.

Input data were prepared with a proprietary program called PCMODEL that is distributed by Serena Software.[54] Except for alkanes the SE values and the heats of formation obtained with PCMODEL are different from those calculated by the MM2(85) force field. The program is relatively convenient to use for simple molecules.

Appendix

Instability in Anomeric Calculations. An instance was found in which different reference bond distances and

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(54) Gilbert, K. PCMODEL, Serena Software, Box 3076, Bloomington, IN 47402-3706.

force constants were calculated by the anomeric correction for the same conformer of a compound of the class RC-$(OR')_3$. The only difference was that alternative numberings were used for the atoms. These bond and force constant differences resulted in different SE values for *the same conformer*, the value being dependent upon the atom numbering, that is, upon the order in which the coordinates were presented. It appears that the algorithm used in adjusting the bond lengths and force constants for anomeric corrections is sensitive to the order in which the components of the anomeric system are introduced. Since the force field is modified relatively extensively "on-the-fly", differences of SE values do not correspond to differences of enthalpies. If the MM2 program is applied to carbohydrates, these matters deserve consideration.

Treatment of Charged Molecules. There are obvious serious problems in performing valid computations with charged molecules. If the dipoles of amides, for example, are represented by point charges, then the very long range and very strong coulombic forces tend to dominate the nonbonded interactions. One consequence is that convergence may fail. A technique that has been used is to turn off Coulombic terms during minimization and then to turn them on for getting the final SE value.[55] If the treatment is extended to ions, the interactions are much larger. Equations 2–6 provide a fundamental statement of the thermodynamics. The equations may be extended to systems of molecules, but it is necessary to take care to define the thermodynamic states correctly. Unless the calculations conform to the requirements of thermodynamics as represented by these equations, the results of any molecular mechanics calculation will be questionable. It may be possible to obtain appropriate averaging of ionic interactions by Monte Carlo or other techniques.

Supplementary Material Available: Tables II, VII, and VIII (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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New Diels–Alder Reactions of (*E*/*Z*)-2'-Methoxy-Substituted 3-Vinylindoles with Carbo- and Heterodienophiles: Regio- and Stereoselective Access to [*b*] Annelated Indoles and Functionalized or [*a*] Annelated Carbazoles

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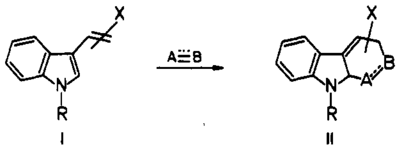
The (*E*/*Z*)-2'-methoxy-substituted 3-vinylindoles **1a,b** react with some carbo- and azodienophiles to furnish new carbazoles and pyridazinoindoles. The conservation of the *E* and *Z* stereochemistry of **1** in these Diels–Alder reactions was investigated, and a mechanistic rationalization is given for the stereoselective and regioselective results observed.

Introduction

Diels–Alder reactions of 2- and 3-vinylindoles as 4π-components are now well-established as versatile procedures for regio- and stereocontrolled syntheses of [*b*] annelated indoles, indole alkaloids,[1–3] and/or carbazoles.[4–8] This methodology should also constitute an interesting synthesis of heteroatom-functionalized carbazoles bearing, e.g., alkoxy, trialkylsiloxy, alkylthio, or amino functional groups. In contrast, the introduction of such polar functionalities onto annelated indoles or carbazoles is generally a tedious task by the more conventional methods known to date. Moreover, compounds of the type II (Scheme I), accessible via Diels–Alder reactions of I, have attracted considerable general interest as building blocks in alkaloid chemistry[9] and, in particular, for the development of pharmacologically active lead substances with antitumor and/or antibiotic properties.[10] The syntheses and exploitation of the Diels–Alder reactivity of heteroatom-functionalized 3-vinylindoles have, as yet, only been sparsely investigated with regard to alkoxy-,[11,12] trialkylsiloxy-,[13] alkylthio-,[14] or amino-functionalized[15,16] 3-vinylindoles.

Scheme I



i.e. X = OAlk, $OSiAlk_3$, SAlk, NR'_2
R = H, Alk, SO_2Ph

Thus, in continuation of our investigations on pericyclic 6-electron processes involving indole derivatives,[4–8,10,11,16]

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