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General Definition of Formal Steric Enthalpy and Applications to Estimating Differences of Enthalpies of Formation

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Formal steric enthalpy (FSE), calculated by molecular mechanics or other suitable procedures, is a defined universal measure of the steric component of the enthalpy of formation of a single conformer. The FSE value of the conformer of lowest energy, the global minimum, is especially important. For many compounds pairwise differences of FSE's of global minima are either equal to the corresponding differences in the gas-phase enthalpies of formation or else may be used to calculate the enthalpy differences. Pairwise difference values may thus be calculable even though individual enthalpies of formation are not known. The double difference of FSE values of two reactant–product (or reactant–transition-state) pairs may provide an estimate of the corresponding double difference of the gas-phase enthalpies of formation even though neither individual nor pairwise differences of enthalpies of formation are available. For many reactions it can be shown that double differences of gas-phase enthalpies are proportional to double differences of free energies of reaction in solution. These relationships provide the basis for the use of molecular mechanics for calculating equilibrium constants and rate constants. Protocols are presented for the general definition of and for the calculation of FSE values.

The purpose of this paper is to present an analysis of the use of pairwise differences and double differences of formal steric enthalpies (FSE's)[1,7-9] as measures of pairwise and double differences of enthalpies of formation in the gas phase. These relationships are important since they provide a reliable means of estimating enthalpy differences of compounds for which experimental enthalpy data are not available.

Double differences of FSE's and in some cases double differences of raw steric energies (SE's) may be used to represent double differences of free energies of formation in solution. I present a rationale that supports this important application and which defines its scope. Historically, double difference methods in the form of linear free energy relationships were devised to cancel out effects that cannot be treated explicitly.[10]

In order to make use of the special capabilities of FSE values, it is necessary to systematize and generalize the definition of formal steric enthalpy, and this task I also address.

Formal steric enthalpy is a defined property of any single conformer. It is the enthalpy due to van der Waals nonbonded interactions plus deformations of bonds, angles, and torsions. It does not include polar effects nor resonance effects; these are to be treated separately. In most applications the conformer of lowest energy, the global minimum, plays an especially important role. Unless otherwise mentioned I shall, therefore, use the unqualified term "FSE" to designate the value for the global minimum.

Steric energies calculated by molecular mechanics have long been used to estimate pairwise differences of enthalpies of formation of conformers.[5] As is well-known, this application is always correct. Double differences of steric energies have been used to estimate relative rates of reactions.[11-23] The limitations of this important application have not been clearly delineated, and I shall discuss them below.

There are two principal advantages of working with formal steric enthalpies (FSE's) rather than with steric energies (SE's). The first is that steric properties in terms of FSE's are defined explicitly and universally through the definitions of steric properties of selected standard conformers, while steric properties in terms of SE's are defined implicitly and locally through some force field. The second is that pairwise and double differences of FSE's, even if not directly equal to corresponding enthalpy differences, may often be corrected so as to give valid estimates of enthalpy differences. Such corrections are less practical with SE's; the range of application is larger for FSE's than for SE's.

The use of steric energies to estimate enthalpies of formation depends on the existence of group additivity relationships which represent the bond energy of a molecule as the sum of contributions of molecular fragments without regard to how they are assembled. Although the underlying premise must have limitations, these methods have a long history of successes in the interpolation and extrapolation of enthalpies of formation and other ther-

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(1) Abbreviations: SE (steric energy), the energy obtained by a molecular mechanics calculation for a particular single conformer by use of a specific force field, excluding polar or resonance components. FSE (formal steric enthalpy), defined by eq 2. FBE (formal bond enthalpy), see eq 2. FSE explicitly excludes polar and resonance effects. The enthalpy of formation of a single conformer, the global minimum, is the sum of FBE + FSE + FPE + FRE, where FPE is the formal polar enthalpy and FRE is the formal resonance enthalpy. For a description of molecular mechanics, see, e.g. ref. 2-6.

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mochemical properties of molecules.[24-29] In the early work steric influences were based on relatively crude corrections.[24-27]

As molecular mechanics developed, increasingly sophisticated use was made of steric energies as measures of steric properties. Allinger and Schleyer were pioneers in this important development. Equation 1 is the defining equation.[4,5,7,30-34] The left-hand side of eq 1 represents

$$\Delta H_f - SM = \sum n_i a_i + SE(\text{global minimum}) \qquad (1)$$

the enthalpy of formation of the single conformer that is the global minimum. H_f is the observed enthalpy of formation; SM is a small statistical mechanical correction for the contributions of other conformers present. The $n_i a_i$ are the group increments; n_i is the number of CH_3 groups or of CH_2 groups, and so on. The a_i are bond contributions of a given group to the enthalpy of formation. The $\Sigma n_i a_i$ term is a bond-energy term.[35] SE is the steric energy calculated by some force field, excluding polar or resonance effects.[1] If present, these latter effects are to be incorporated as corrections to the left-hand side of eq 1.

Equation 1 reproduces the enthalpies of formation of all but highly crowded alkanes and cycloalkanes within better than 0.4 kcal/mol.[5,7,8,33] The reproducibility for certain other families of compounds may be comparable.

Equation 2 is an alternative to eq 1. The a_i increments and the SE values of eq 1 are *force field dependent* while the c_i and the FSE values of eq 2 are universal; they are defined in terms of standards.[7-9,34] $\Sigma n_i c_i$ is FBE, the formal bond enthalpy, the enthalpy of formation of a hypothetical strain-free conformer.[31]

$$\Delta H_f - SM = \sum n_i c_i + FSE(\text{global minimum}) \qquad (2)$$

The limitations of SE values have sometimes been circumvented by the calculation of enthalpies of formation, which are then converted to "strain energies".[5,31,36-38] The use of FSE values is a generalization of this approach; a FSE value is an estimate of single conformer strain energy.[31] The use of FSE values is general since, as will be shown below, FSE's can be calculated even though enthalpy of formation data are not available.

In the general case the left-hand side of eq 2 may need to be corrected for polar effects (formal polar enthalpy) and resonance effects (formal resonance enthalpy). If a force field incorporates polar terms or resonance terms, then there should be provision to report these separately. The SE values addressed in this paper must have the polar and resonance components removed; their contributions to the enthalpy of formation are to be treated separately.

Equation 2 has three distinct uses, viz. to calibrate the c_i values, to calculate FSE values, and to calculate ΔH_f values. Moreover the estimation of differences of enthalpies of formation in terms of differences of FSE values is based on eq 2.

The use of eq 2 to calibrate c_i values may be illustrated with alkanes. Examples of the other uses can be found below. The composition of any alkane or cycloalkane may be described in terms of four groups, CH_3, CH_2, CH, and C, and specification of the formal bond enthalpy requires four group increments, $c(CH_3)$, $c(CH_2)$, $c(CH)$, and $c(C)$. A widely used convention assigns FSE = 0 to the extended conformer of any *n*-alkane.[39] Two *n*-alkanes suffice to define $c(CH_3)$ and $c(CH_2)$; *n*-butane and *n*-octane are suitable. The necessary SM values may be estimated by obtaining the steric energies of all important conformers or by equivalent approximation methods.[7,40] The enthalpies of formation are taken from appropriate compilations. This gives two instances of eq 2 having as unknowns $c(CH_3)$ and $c(CH_2)$, whose values are now defined.[7]

In order to define $c(CH)$ and $c(C)$ we must select appropriate molecules and assign reasonable FSE values. We have used FSE = 0.7 kcal/mol for isoalkanes and 1.4 for neoalkanes; 2-methylbutane and 2,2-dimethylbutane are suitable. The consequent FSE values of crowded alkanes are only moderately sensitive to these assigned FSE values.[7] Although the FSE values of isobutane and of neopentane may reasonably be assigned as zero, these compounds are less suitable standards since their steric energies and thermochemical properties are atypical.[7,28,29]

In practice it is preferable to base the c_i values on a broad series of alkanes in order to average out errors in experimental values of enthalpies of formation. Table I summarizes the c_i values of alkanes and Table II lists a representative set of standards for alkanes.[39]

The use of eq 2 to calculate "experimental" FSE values is straightforward. The only problem is to estimate the SM values. It is often difficult to determine the origin of published SM values. The most direct method is to obtain SE values for all low energy conformers and to calculate the SM value from the Boltzmann distribution. We have provided a general way to get approximate values for alkanes and methyl-substituted alkanes.[7,40] In other cases our estimates have been made by analogy or by limited information on the energies of separate conformers. For many compounds the error in the SM value is likely to be smaller than the experimental error in the enthalpy of formation.

The use of eq 2 to estimate enthalpies of formation is based on the independent calculation of FSE values by molecular mechanics or other suitable procedure. In view of the accuracy attainable in calculated enthalpies of formation,[5] better methods of estimating SM values are worth further investigation.

FSE values may be calculated from SE values by eq 3,

$$FSE = SE - \sum n_i d_i \qquad (3)$$

which follows as a combination of eq 1 and 2 with $d_i = c_i - a_i$. The d_i values for a given force field can be based on

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Table I. Group Increments for Calculating Formal Bond Enthalpy

Alkanes[a]	
C C H H H	-10.064 ± 0.02
C C C H H	-5.141 ± 0.01
C C C C H	-2.19 ± 0.09
C C C C C	-0.22 ± 0.17
Alkenes[b]	
C CDH H H	-10.22 ± 0.10
C C CDH H	(-5.141)[c]
C C C CDH	1.95 ± 0.13
C C C C CD	-0.60[d]
CDCDH H	6.30 ± 0.07
CDC CDH	8.77 ± 0.07
CDC C CD	10.16 ± 0.46
Alcohols and Ethers[e]	
C H H H O	-7.10 ± 0.42
C C H H O	(-5.141)[c]
C C C H O	-4.14 ± 0.38
C C C C O	-3.96 ± 0.87
O C H	-40.81 ± 0.26
O C C	-30.18 ± 0.49
Aldehydes and Ketones[f]	
C CDH H H (C CKH H H)	-10.25 ± 0.3
C C CDH H (C C CKH H)	(-5.141)[c]
C C C CDH (C C C CKH)	-1.36 ± 0.5
C C C C CD (C C C C CK)	+1.85 ± 0.5
CDC H OD	-29.58 ± 0.2
CDC C OD	-31.43 ± 0.2
Phenyl C_6H_5R[g]	
C CAH H H	-10.30
C C CAH H	(-5.141)[c]
C C C CAH	-1.16
C C C C CA	2.62
C6H5	22.23
(H	-2.41)[k]
Acids and Esters[h]	
C CDH H H (C CEH H H)	-10.40 ± 0.3
C C CDH H (C C CEH H)	(-5.141)[c]
C C C CDH (C C C CEH)	-5.02 ± 0.5
CDC ODOH[i]	-92.53 ± 0.3
CDC OCOD[j]	-81.47 ± 0.2

[a] All entries are c_i values in kcal/mol, 25 °C, recalculated, and using two sets of data, those from ref 29 and those from ref 45. Alkane c_i values are based on alkanes listed in Table II. Values for c(C C H H H) and c(C C C H H) were calculated from data for the five n-alkanes alone. Then the values for c(C C C C H) and c(C C C C C) were calculated as simple averages. The values are in accord with those reported in ref 7 and 8. [b] Recalculated from data of ref 45 based on compounds listed in Table II. The olefin data of ref 29 appear to be less reliable. The relationships between these values and those of ref 8 are described in the text. Except for C C C CDH and C C C C C the values are concordant with those in ref 8. [c] Assigned value. [d] Based on only one compounds. [e] Recalculated from the data of ref 29 from the compounds listed in Table II. The ref 45 values are comparable. The relationships between these values and those of ref 8 are described in the text. The values are concordant. [f] Calculated from the data of ref 45 from the compounds shown in Table II. In parentheses are notations based on use of CK to designate the carbonyl sp^2 carbon atom of an aldehyde or a ketone. See text. [g] Calculated from the data in refs 29 and 45, based on benzene, toluene, ethylbenzene, n-propylbenzene, isopropylbenzene, and *tert*-butylbenzene. The vallues reproduce data for dimethylbenzenes, trimethylbenzenes, and methylethylbenzenes except for 1,2,3-trimethylbenzene within a maximum error of 0.3 kcal/mol. [g] Assigned value. See text. [h] Calculated from the data of ref 45 on the basis of the compounds listed in Table II. In parentheses are notations based on use of CE to designate the carbonyl carbon atom of an acid or an ester. See text. [i] COOH group. [j] COOC group. [k] For each extra hydrogen atom removed add 2.41. For example, the enthalpy of formation of 1,3-dimethylbenzene is 22.23 + 2.41 − 2(10.30) = 4.04(4.12 observed). Beckhaus prefers to use the alkane increments for the α carbon atoms; *tert*-butylbenzene then has FSE = 2.8 kcal/mol.[46]

the minimal set of standards used for the c_i values; there is no need to use families of compounds. Table II suggests suitable standards for several sets of compounds including the alkane set. Two force fields that give acceptable enthalpies of formation of representative compounds by eq 1 or 2 will give closely similar values of FSE by eq 3.[7,38]

Equation 3 is of great potential value to anyone who wishes to investigate the effect of varying parameters of a force field. It is difficult to make sense out of comparisons of SE values that result from variants of a force field, but if all data are converted to FSE values through appropriate d_i sets, then the FSE values will serve as valid measures of the resulting trends.

Since FSE values are universally defined for a given family of compounds, it becomes possible to accumulate the results of molecular mechanics studies in the form of compilations of tables of steric properties of conformers. FSE values are, of course, applicable to all conformers, not just the global minimum.

Calculated FSE values should be equal to experimental FSE values. In fact a comparison of calculated FSE values with experimental FSE values provides a more rigorous test of the performance of a force field than does a comparison of enthalpies of formation since the latter trend to be dominated by the formal bond enthalpy term.

Significance of Pairwise Differences of FSE Values. Equations 4 and 5 define the relationships between pairwise differences of formal steric enthalpies and pairwise differences of enthalpies of formation. It is assumed

$$\Delta \mathrm{FSE} = \mathrm{FSE(b)} - \mathrm{FSE(a)} \tag{4}$$

$$\Delta H_f = (\textstyle\sum n_i c_i)_b - (\sum n_i c_i)_a + \Delta \mathrm{FSE} + \Delta \mathrm{SM} \tag{5}$$

$$\Delta H_f = \Delta \mathrm{FBE} + \Delta \mathrm{FSE} + \Delta \mathrm{SM} \tag{6}$$

that the FSE values have been calculated by eq 3 from a force field that meets the requirement of eq 1 or 2. Comparable equations have been described earlier on the basis of SE values. For SE's $\sum n_i a_i$ is to be used in place of $\sum n_i c_i$ in eq 4–6.[13–15] Equation 5 shows that either ΔFSE or ΔSE is equal to ΔH_f apart from a small SM correction, providing that the two $\sum n_i c_i$ ($\sum n_i a_i$) terms cancel, as they do for pairs of conformers.

If the terms do not cancel, it still may be possible to calculate the difference of the $\sum n_i c_i$ terms (but not so

Table II. Proposed Standards for Defining FSE Values[a]

	molecule	assigned FSE value	SM	$-\Delta H_f^{\circ}$ [a]	
Alkane d_i[b]					
C C H H H	butane	0	0.27	30.15	30.23
C C C H H	octane	0	1.19	49.82	49.83
C C C C H	2-methylbutane	0.7	0.09	36.92	36.76
C C C C C	2,2-dimethylbutane	1.4	0.00	44.35	44.55
Alkane c_i, Above Plus					
	pentane	0	0.50	35.00	35.01
	hexane	0	0.73	39.96	39.94
	heptane	0	0.96	44.88	44.81
	2-methylpentane	0.7	0.26	41.66	41.78
	2-methylhexane	0.7	0.50	46.59	46.51
	2-methylheptane	0.7	0.73	51.50	51.48
	2,2-dimethylpentane	1.4	0.17	49.27	49.38
	2,2-dimethylhexane	1.4	0.42	53.71	53.68
Alcohol–Ether d_i					
O C H	1-butanol	0.0	0.33	65.59	65.73
O C C	diethyl ether	0.0	0.50	60.28	60.16
C H H H O	methyl ethyl ether	0.0	0.27	51.73	51.72
C C C H O	2-butanol	0.15	0.25	69.86	70.46
C C C C O	2-methyl-2-butanol	0.85	0.09	78.65	79.06
Alcohol–Ether c_i, Above Plus					
	methanol	0.0	0.0	48.08	48.01
	ethanol	0.0	0.0	56.12	56.12
	1-propanol	0.0	0.09	61.55	60.90
	2-propanol	0.0	0.0	65.15	65.13
	methyl *n*-propyl ether	0.0	0.73	56.82	56.86
	methyl isopropyl ether	1.12	0.09	60.24	60.23
	diisopropyl ether	2.24	0.29	76.20	76.20
	methyl *tert*-butyl ether	1.94	0.0	69.85	67.78
Olefin d_i					
CDCDH H	ethylene	0.0	0.0	−12.50	−12.48
CDC CDH	1-butene	0.0	0.0	0.03	−0.10
CDC C CD	*trans*-3-hexene	0.0	0.0	13.01	13.00
C CDH H H	*trans*-2-butene	0.0	0.0	2.67	2.92
C C C CDH	3-methyl-1-butene	0.15	0.0	6.92	6.55
C C C C CD	3,3-dimethyl-1-butene	1.2	0.0	10.31	14.51
Olefin c_i, Above Plus					
	propene	0.0	0.0	−4.88	−4.83
	1-pentene	0.0	0.06	5.00	5.23
	1-hexene	0.0	0.29	9.96	9.94
	trans-2-pentene	0.0	0.0	7.59	7.82
	trans-2-hexene	0.0	0.06	12.88	12.88
	3-methyl-1-pentene	0.15	0.38	10.76	11.83
	trans-4-methyl-2-pentene	0.0	0.0	12.99	14.70
	2-methyl-1-propene	0.0	0.0	4.04	4.0j
	2-methyl-1-butene	0.2	0.0	8.68	8.51
	2-methyl-1-pentene	0.2	0.0	12.49	14.20
Aldehyde–Ketone d_2					
CDC H OD	propanal	0.0	0.0	45.90	44.78
CDC C OD	3-pentanone	0.0	0.0		61.75
C CDH H H	2-butanone	0.0	0.0	56.97	57.55
C C C CDH	3-methyl-2-butanone	0.0	0.20		62.71
C C C C CD	3,3-dimethyl-2-butanone	0.0	0.0		69.26
Aldehyde–Ketone c_i, Above Plus					
	Acetaldehyde	0.0	0.0	39.76	39.62
	acetone	0.0	0.0	52.00	51.91
	butanal	0.0	0.05	49.00	49.59
	2-methylpropanal	0.0	0.0		51.52
	pentanal	0.0	0.28	54.45	55.09
	2-pentanone	0.0	0.12	61.82	61.92
	2-hexanone	0.0	0.35		66.87
	3-hexanone	0.0	0.35		66.51
	2-methyl-3-pentanone	0.0	0.0		68.37
	2,2-dimethyl-3-pentanone	0.0	0.0		74.97
	2,4-dimethyl-3-pentanone	0.0	0.0		74.40
Acid–Ester d_i					
CDC ODOH	propanoic acid	0.0	0.0		−107.09
CDC OCOD	ethyl propanoate[c]	0.85	0.0		−110.80
C CDH H H	ethyl acetate[c]	0.85	0.0	−105.86	−106.14
C C C CDH	ethyl 2-methylbutanoate[c]	1.38	0.23		−124.86
C C C C CD	ethyl 2,2-dimethylpropanoate[c]	1.38	0.0		−128.10
Acid–Ester c_i, Above Plus					
	acetic acid	0.0	0.0	−103.93	−103.27
	methyl acetate	0.85	0.0		−97.99
	butanoic acid	0.0	0.06		−113.74
	pentanoic acid	0.0	0.29		−117.13
	n-butyl acetate	0.85	0.27		−116.06
	hexanoic acid	0.0	0.52		−122.75
	methyl pentanoate	0.85	0.29		−112.69
	ethyl pentanoate	0.85	0.29		−121.15
	methyl 2-methylbutanoate	1.38	0.23		−117.68
	ethyl 3-methylbutanoate	1.01	0.03		−119.00
	methyl hexanoate	0.85	0.52		−118.02
Alkylbenzene d_i					
C6H5	ethylbenzene	0.0	0.0	−7.12	−6.98
H CA	benzene	0.0	0.0	−19.82	−19.80
C CAH H H	toluene	0.0	0.0	−11.95	−11.97
C C C CAH	isopropylbenzene	0.0	0.0	−0.94	−0.96
C C C C CA	*tert*-butylbenzene	1.0	0.0		5.40
Alkylbenzene c_i, Above Plus					
	n-propylbenzene	0.0	0.0	−1.87	−1.87
	sec-butylbenzene	0.0	0.0		4.13
	isobutylbenzene	0.2	0.0		5.14

[a] kcal/mol values in first column from ref 29, in second column from ref 45. In each series the C C H H X group is assigned the value for C C C H H. [b] The d_i values may be calculated from eq 3, conveniently in the order indicated. In every case the steric energy to be used is for the conformer of lowest energy. [c] The methyl esters are to be used for d_i calibrations.

readily of $\Sigma n_i a_i$ terms). A specific example is the application to amides **1** and **2**. The ΔSM term may be estimated either by calculating the energies of all important conformers or by analogy with other compounds. The ΔFBE difference here is c(C C C C H) − c(C C C C H) − c(C C H H H).[39] Since the necessary c_i values are available from alkane data, ΔH_f can be calculated even though data are not available for calculating the individual enthalpies of formation of these amides; ΔH_f data are not available for representative amides and therefore the necessary $c(CONHCH_3)$ cannot be calculated.

$$\underset{\mathbf{1}}{(CH_3)_2CHCH_2CONHCH_3} \qquad \underset{\mathbf{2}}{CH_3(CH_2)_2CONHCH_3}$$

Compounds **3** and **4** illustrate a different case; the α carbon atoms are now respectively secondary and tertiary. Unless estimates of sufficient accuracy can be made for the c_i values for α carbon atoms, it is not possible in principle to calculate the differences of enthalpies of formation for such molecules. It is possible to make comparisons in two separate series, one based on amides with α-CH_2 groups, the other amides with α-CH groups.

$$\underset{\mathbf{3}}{(CH_3)_2CHCONHCH_3} \qquad \underset{\mathbf{4}}{CH_3CH_2C(CH_3)_2CONHCH_3}$$

Double Differences of FSE's. The usual application of double differences is to reactant–product pairs or to reactant–transition-state pairs. In terms of transition-state theory relative rate constants may be expressed by eq 7.

$$\log (k_2/k_1) = (\Delta G^{\ddagger}{}_1 - \Delta G^{\ddagger}{}_2)/2.303RT \qquad (7)$$

The quantity to be estimated is $(\Delta G^{\ddagger}{}_2 - \Delta G^{\ddagger}{}_1)$ for the reaction in solution. It may be shown that this in turn is often proportional to the gas-phase enthalpy double difference. This proportionality makes possible the use of molecular mechanics to calculate reaction rates by eq 17 below, which is a linear free energy relationship. The left-hand side of eq 17 is log k(rel) corrected if necessary for minor polar effects ($\rho\sigma_i$) and for multiple reactant conformers and multiple transition states (r).[41]

The derivation of eq 17 will be based on a specific example. Let eq 8 and 9 represent reactions in which the functional group X is converted into the transition-state group Y. For modeling esterification in methanol X would be COOH and Y might be the $C(OH)_2OMe$ group; R1 and R2 are the reactant acids while T1 and T2 are models of the transition states.

$$\underset{\text{R1}}{(CH_3)_2CHCH_2X} + MeOH \rightarrow \underset{\text{T1}}{(CH_3)_2CHCH_2Y} \qquad (8)$$

$$\underset{\text{R2}}{CH_3CH_2CH(CH_3)X} + MeOH \rightarrow \underset{\text{T2}}{CH_3CH_2CH(CH_3)Y} \qquad (9)$$

On the basis of eq 5, the gas-phase value of the enthalpies of activation may be represented by eq 10 and 11. The double difference of enthalpies of formation $\Delta\Delta H^{\ddagger}{}_{21} = \Delta H^{\ddagger}{}_2 - \Delta H^{\ddagger}{}_1$ is given by eq 12. $\Delta FSE_2 = FSE(T2) - FSE(R2)$, and similarly for ΔFSE_1.

$$\Delta H_f{}^{\ddagger}{}_1 = \mathrm{FSE(T1)} - \mathrm{FSE(R1)} + c(\mathrm{C\ C\ C\ H\ H\ }) - c(\mathrm{C\ C\ CDH\ H\ }) - \Delta H_f(\mathrm{MeOH}) + \mathrm{SM\ terms} + c[\mathrm{Y}] - c[\mathrm{X}] \qquad (10)$$

$$\Delta H_f{}^{\ddagger}{}_2 = \mathrm{FSE(T2)} - \mathrm{FSE(R2)} + c(\mathrm{C\ C\ C\ C\ H\ }) - c(\mathrm{C\ C\ C\ CDH\ }) - \Delta H_f(\mathrm{MeOH}) + \mathrm{SM\ terms} + c[\mathrm{Y}] - c[\mathrm{X}] \qquad (11)$$

$$\Delta\Delta H_f{}^{\ddagger}{}_{21} = \Delta \mathrm{FSE}_2 - \Delta \mathrm{FSE}_1 + c(\mathrm{C\ C\ C\ C\ H\ }) - c(\mathrm{C\ C\ C\ CDH\ }) - c[\mathrm{C\ C\ C\ H\ H\ }] + c[\mathrm{C\ C\ CDH\ H\ }] + \mathrm{SM\ terms} \qquad (12)$$

Examination of eq 12 shows clearly one limitation of the method. If two reactions under comparison incorporate exactly the same groups, then the c_i terms of eq 12 drop identically. In that case $\Delta\Delta H^{\ddagger}{}_{21} = \Delta FSE_2 - \Delta FSE_1$ if the SM terms cancel. Moreover, $\Delta\Delta H^{\ddagger}{}_{21} = \Delta SE_2 - \Delta SE_1$ and the gas-phase difference in enthalpies of activation is correctly estimated either by the double difference of formal steric enthalpies or of raw SE values.[13-15] However, if the groups do not cancel, as they do not in the example, then comparisons are limited to series for which the differences are constant throughout unless it is possible to derive sufficiently good estimates of the missing c_i values.

For esterification the conclusion is that the correlations can treat all RCH_2COOH as one family, all $R_2CHCOOH$ as another family, and all R_3CCOOH as a third family. Similar considerations apply to other types of reactions. It is not correct to use mixtures of families unless a proper correction can be applied for unbalanced group increments.

For calculation of equilibrium constants the $\Delta\Delta$SM term has the usual significance of representing a correction to the enthalpy terms. However, for reactions the significance is different. If there are several reactant conformers and several conformers of the transition state, then the system consists of a set of reactant conformers that may react through a series of channels (transition state conformers). We have shown elsewhere how to calculate the correction, designated as r in eq 16 and 17;[41] r will not usually exceed ±0.3 and may often be neglected.

We consider next the enthalpy of solvation. For a given reactant or transition state, it is permissible to dissect the enthalpy into three components, one for the R group, one for the X group or the Y group, and an interaction correction for differences in solvation from one molecule to the next due to the way in which the presence of X modifies the solvation of R and vice versa. This dissection is represented by eq 13 for R_1X and by eq 14 for the double difference. As can be seen from eq 14, it is only the "interaction" terms that do not cancel.

$$\Delta H(\mathrm{solv},R_1X) = \Delta H(\mathrm{solv},R_1) + \Delta H(\mathrm{solv},X) + \Delta H(\mathrm{solv},R_1\text{–}X) \qquad (13)$$

$$\Delta\Delta H^{\ddagger}{}_{21}(\mathrm{soln}) = \Delta\Delta H^{\ddagger}(\mathrm{gas}) + \Delta H(\mathrm{solv},R_2\text{–}Y) - \Delta H(\mathrm{solv},R_2\text{–}X) - \Delta H(\mathrm{solv},R_1\text{–}Y) + \Delta H(\mathrm{solv},R_1\text{–}X) \qquad (14)$$

For any molecule there will be a relationship between the area of the interaction between R and X or Y and the magnitude of the interaction term. ΔFSE_i also depends on the same area of interaction. As a first-order approximation $\Delta H(\mathrm{solv},R_i\text{–}Y) - \Delta H(\mathrm{solv},R_iX)$ will be proportional to ΔFSE_i. This model explicitly cancels out the presumably larger "backside within R" contributions to individual FSE values.

In eq 15 this proportionality is represented as f(solv), with f(solv) some relatively small fraction.

$$\Delta\Delta G^{\ddagger}{}_{21}(\mathrm{soln}) = (\Delta FSE_2 - \Delta FSE_1)[1 + f(\mathrm{solv}) + Tf(\mathrm{entropy})] + \text{polar and channel corrections} \qquad (15)$$

Because of similarities of structures among reactants and products or transition-state models, double differences of gas-phase or of solution-phase entropies of reaction should

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[41] DeTar, D. F. *J. Org. Chem.* **1986**, *51*,.

largely cancel, unless rings are formed or opened. Ring-closure reactions require direct estimation of entropies of activation.[15] To the extent that double differences of entropies do not cancel they, too, may in the first approximation tend to be proportional to $\Delta\mathrm{FSE}_i$. In eq 15 this is expressed as f(entropy).

It is useful to incorporate polar[42] and "channel" (r)[41] corrections on the left to emphasize that they have been treated explicitly and are not a part of the FSE formalism. Equation 17 puts eq 16 in the form of a conventional linear

$$\log k(\mathrm{rel})_i - r - \rho\sigma_i = a + \mathrm{FSE}_i[1 + f(\mathrm{solv}) + Tf(\mathrm{entropy})]/2.303RT \quad (16)$$

$$\log k(\mathrm{rel})_i - r - \rho\sigma_i = a + b\mathrm{FSE}_i \quad (17)$$

free energy relationship. For esterification this is a generalization of the Taft equation[42,43] in which the steric component has been calculated directly from molecular structure by use of molecular mechanics. A plot of ($\log k_i - r_i - \rho\sigma_i$) vs. $\Delta\mathrm{FSE}_i$ will give a straight line for a given family of compounds with a slope of $-[1 + f(\mathrm{solv}) + Tf(\mathrm{entropy})]/2.303RT$. The slope will have the value of $-1/2.303RT$ only if solvation and entropic effects cancel and if the model correctly estimates the steric effects present in the transition state. A model that consistently underestimates the steric effects in the transition state or that consistently overestimates the effects will also affect the slope but may not affect the correlation.

Equation 16 provides the theoretical basis for relating reaction equilibria and rates to differences of steric energies or of formal steric enthalpies as calculated by molecular mechanics.

Protocols for Defining FSE Values. Although four groups suffice for specifying the formal bond enthalpy of an alkane, the number required increases rapidly as functional groups are added. We need, therefore, a general method for defining groups and for selecting standards and assigning suitable FSE values. An indication of the types of groups required may be seen from Benson's tabulations.[27] The Benson additivity scheme is based on groups defined in terms of nearest neighbors. That is, a group is defined as a central atom plus those atoms directly bonded. In the Benson notation the groups for alkanes are $\mathrm{C{-}(H)_3(C)}$, $\mathrm{C{-}(H)_2(C)2}$, $\mathrm{C{-}(H)(C)_3}$, and $\mathrm{C{-}(C)_4}$.

The Benson notation is reasonably consistent and comprehensive, but the subscripts and parentheses make usage somewhat awkward. Since it will be necessary to resort to computer techniques, we need a notation that is rigorously unambiguous and simple. This may be achieved by using two-character symbols for all atoms (blank being an acceptable second character) and by writing out the ligands in strict alphabetic order. Following the Benson notation in spirit, $\mathrm{sp^2}$ C becomes CD, sp C becomes CT, aromatic C becomes CA, and similarly for N and O. With this notation $\mathrm{CH_3}$ = (C C H H H), $\mathrm{CH_2}$ = (C C C H H) (methylene group of an alkane), and $\mathrm{CH_2}$ = (CDCDH H) for the vinyl methylene group. The $\mathrm{CH_3}$ group of $\mathrm{CH_3O}$ becomes (C H H H O).

Table I shows the complete set of groups needed to describe alkanes, alkenes, alcohols and ethers, aldehydes and ketones, and acids and esters. For all examples the c_i of a group is defined to represent the contribution of the atom indicated plus that of the attached hydrogen atoms. The atomic level of detail is not always necessary or useful. A group may be taken as any unit that is constant throughout a series as is illustrated by the phenyl group in Table I.

In an earlier paper we defined groups for alcohols and ethers differently. Since six groups, in addition to the alkane groups, are needed to represent alcohols and ethers, but only five are independent, it is necessary either to modify definitions so as to delete one group or else to assign an arbitrary value to one. In the earlier paper we deleted a group.[8] The Benson convention is to assign an arbitrary value to one of the groups.[27] I now find that the Benson approach is more convenient. Benson assigns an arbitrary value to the methyl group. It seems better to assign a value to the methylene group instead since it can appear in many compounds and since it is nearer the center of the series. This redundancy problem occurs frequently. The convention is that c(C C H H X) = c(C C C H H) for any X.

A potential limitation of the nearest neighbor approximation is that the bonding situation about an $\mathrm{sp^3}$ C is not necessarily the same for all sets of nearest neighbors. For example, in terms of nearest neighbors the carbon of the CC=O sequence is assumed to make the same contribution to the FBE as does the carbon of the CC=C sequence. In both the critical nearest neighbor is an $\mathrm{sp^2}$ carbon atom. As for steric effects, it appears best to define the steric effect of an $\mathrm{sp^2}$ carbon atom as independent of whether it is part of a carbonyl group or part of an olefin. This means that it may be necessary in a few cases to distinguish among certain atoms having the same nearest neighbors and to assign to them individual c_i values.

The limited available information is summarized in Table I. Within error limits all of the c(C CDH H H) values are the same. The c(C C CDH H) values are all the same by assignment. The c(C C C CDH) values are −5.20 for esters (two examples), −1.36 for aldehydes and ketones (four examples), and −1.95 for alkenes (three examples). The data for the c(C C C C CD) values are still fewer, and there are serious discrepancies. A way to designate these modified groups is to adopt separate symbols for the several types of $\mathrm{sp^2}$ carbon. For instance, let CD stand for the olefinic carbon, CE for the ester carbon, and CK for the carbonyl carbon of an aldehyde or a ketone. The three special values are then c(C C C CDH) = −1.95, c(C C CEH) = −5.20, and c(C C C CKH) = −1.36. For consistency all corresponding atoms in a set need to be changed as shown in parentheses in Table I.

Procedures for Assigning FSE Values to Standard Conformers. We have treated this problem in earlier papers.[7-9] A practical approach bases FSE values on estimates of gauche interaction enthalpies as derived by use of one or more force fields. The least assumptions are involved if conformers of lowest formal steric enthalpy are chosen as standards.

Table II includes examples that illustrate the general procedure for selecting standards. For use with eq 3 it should suffice to select a minimum set. For calculating c_i values it is advisable to select a larger set and to use averaging. The approach illustrated in the examples may readily be extended to other families.

For the calculation of the d_i correction terms of eq 3 the compounds listed in the first series should prove convenient. Since SE values may be determined to any desired level of precision, there is no need to use redundant standards, except perhaps as a check.

In Table II there is a considerable emphasis on deriving the c_i values for calculating enthalpies of formation, but the selection of standards for calculating the d_i terms is equally (or more) important. Table II lists all the com-

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[42] DeTar, D. F. *J. Am. Chem. Soc.* **1982**, *104*, 7205.

[43] Taft, R. W., Jr. In *Steric Effects in Organic Chemistry*; Newman, M. S., Ed.; Wiley: New York, 1956; p 556.

pounds used to derive the c_i values listed in Table I.

Different procedures were followed in calculating c_i values in the different series. The alkane $c(\mathrm{C\ C\ H\ H\ H})$ and $c(\mathrm{C\ C\ C\ H\ H})$ values are based on just the *n*-alkanes in order to provide highest accuracy for these important values. The other two alkane values were determined as simple averages of residuals.

For the alcohols and the alkenes it was more convenient to use an overall least-squares adjustment.[44] For the other compounds it was possible to examine the residuals remaining after subtracting out the c_i values of the standard groups. The remaining c_i values could then be obtained as averages from selected residuals. The results were checked by calculating the ΔH_f values; there are a few fairly large discrepancies. Among the reported compounds the largest deviations of calculated ΔH_f are 0.7 kcal/mol. A few omitted compounds showed discrepancies of the order of 4 kcal/mol; these are presumably errors because the data also fail the test of internal consistency. For purposes of illustration a few of these discordant values have been left in Table II, although the discordant series were not used to get the reported C_i values.

Relationships between c_i Values. The relationships between the c_i values in the earlier study[7,8] and the present values are as follows:

$$c(\mathrm{CH_3O}) = c(\mathrm{C\ H\ H\ H\ O}) + 0.5c(\mathrm{O\ C\ C})$$

$$c(\mathrm{CH_2O}) = -5.141 + 0.5c(\mathrm{O\ C\ C})$$

$$c(\mathrm{CHO}) = c(\mathrm{C\ C\ C\ H\ O}) + 0.5c(\mathrm{O\ C\ C})$$

$$c(\mathrm{CO}) = c(\mathrm{C\ C\ C\ C\ O}) + 0.5c(\mathrm{O\ C\ C})$$

$$c(\mathrm{HO}) = c(\mathrm{O\ C\ H}) - 0.5c(\mathrm{O\ C\ C})$$

$$c(\mathrm{CH_3}\text{-}\alpha) = c(\mathrm{C\ CDH\ H\ H}) - 10.00 + 5.14$$

$$c(\mathrm{CH_2}\text{-}\alpha) = -10.00$$

$$c(\mathrm{CH}\text{-}\alpha) = c(\mathrm{C\ C\ C\ CDH}) - 10.00 + 5.14$$

$$c(\mathrm{C}\text{-}\alpha) = c(\mathrm{C\ C\ C\ C\ CD}) - 10.00 + 5.14$$

$$c(\mathrm{{=}CH_2}) = c(\mathrm{CDCDH\ H})$$

$$c(\mathrm{{=}CCH}) = c(\mathrm{CDC\ CDH}) + 10.00 - 5.14$$

$$c(\mathrm{{=}C_2}) = c(\mathrm{CDC\ C\ CD}) + 20.00 - 10.28$$

Two sets of programs have been developed to aid in identification of representative groups and in systematic assignment of FSE values to standards.[47]

Registry No. 2-Methylbutane, 78-78-4; 2,2-dimethylbutane, 75-83-2; 2-methylpentane, 107-83-5; 2-methylhexane, 591-76-4; 2-methylheptane, 592-27-8; 2,2-dimethylpentane, 590-35-2; 2,2-dimethylhexane, 590-73-8; 2-butanol, 78-92-2; 2-methyl-2-butanol, 75-85-4; methyl isopropyl ether, 598-53-8; diisopropyl ether, 108-20-3; methyl *tert*-butyl ether, 1634-04-4; 3-methyl-1-butene, 563-45-1; 3,3-dimethyl-1-butene, 558-37-2; 3-methyl-1-pentene, 760-20-3; 2-methyl-1-butene, 563-46-2; 2-methyl-1-pentene, 763-29-1; ethyl propanoate, 105-37-3; ethyl acetate, 141-78-6; ethyl 2-methylbutanoate, 7452-79-1; ethyl 2,2-dimethylpropanoate, 3938-59-2; methyl acetate, 79-20-9; butyl acetate, 123-86-4; methyl pentanoate, 624-24-8; ethyl pentanoate, 539-82-2; methyl 2-methylbutanoate, 868-57-5; ethyl 3-methylbutanoate, 108-64-5; methyl hexanoate, 106-70-7; *tert*-butylbenzene, 98-06-6; isobutylbenzene, 538-93-2.

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Notes

The Reaction of Amines with Methylene Chloride. Evidence for Rapid Aminal Formation from *N*-Methylenepyrrolidinium Chloride and Pyrrolidine

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Several papers dealing with the reaction of amines with methylene chloride have recently appeared in the literature.[1-8] The conclusions drawn by the authors are markedly different. Some chemists report that the reaction of methylene chloride with amines is negligible or nonexistent at atmospheric pressure,[3,4] while others recommend caution when using this solvent for extractions of amines.[1,2] Here, we shall attempt to dispel the myth that methylene chloride is unreactive with amines by providing additional evidence for the rapid reaction of methylene chloride with a secondary amine at room temperature and atmospheric pressure. In addition, this note describes studies which establish that, in methylene chloride or chloroform, the reaction of a tertiary chloromethylamine (1-methylenepyrrolidinium chloride) with pyrrolidine is rapid.

The rate of the reaction of methylene chloride with a

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