Treatment of Boc-alanyl-*p*-(acyloxy)benzhydrylamine Resin with Base and Nucleophile. A. Stability Test. Samples of Boc-Ala-*p*-(acyloxy)benzhydrylamine resin (100 mg each, 0.4 mmol/g) prepared from method D were treated in separate experiments with 1-hydroxybenzotriazole, diisopropylethylamine, triethylamine, or pyridine in either CH_2Cl_2 or DMF. After 24 h, resins were washed with DMF, CH_2Cl_2, and CH_3CN, and Ala left on the resin was determined by the quantitative ninhydrin test after the removal of the (*tert*-butyloxy)carbonyl and neutralization by diisopropylethylamine. Filtrates were evaporated, hydrolyzed in HCl-propionic acid (1:1, v/v) at 130 °C for 4 h, and quantitated by the amino acid analyzer. The results are summarized in Table IV.

B. Cleavage Reactions. Alanyl resin (100 mg each, 0.4 mmol/g) were treated with 3 equiv each of 95% NH_2NH_2, $HONH_2 \cdot HCl$ with Et_3N, H_2O_2–Na_2CO_3 (pH 11.5)–dioxane–H_2O (1:1), and tetrabutylammonium cyanide in 50% MeOH–DMF for 1 h at 24 °C. Analysis of the cleavage yield was similar for A. The results are summarized in Table III.

Similarly, resins **12**–**15** (100 mg each) were treated with 5 mL of HF–*p*-cresol (9:1, v/v) at 0 °C for 1 h. Separately, each resin was also treated with the gradative deprotection method of 5 mL of HF–dimethyl sulfide–*p*-cresol (25:65:10, v/v) for 2 h and washed with CF_3CO_2H–CH_2Cl_2 (1:1, v/v) 3× (2 min), CH_2Cl_2 3× (1 min), DMF 3× (1 min), 5% NH_2NH_2–DMF 1× (30 min), and DMF 3× (1 min). The resins resulted from both treatments were then hydrolyzed in 12 N HCl–phenol–HOAC (2:1:1, v/v) for 24 h. The cleavage yield from the resin was calculated by 100% − % remaining on the resin. The results are summarized in Table II.

Synthesis of Test Peptides. General Procedure. The syntheses of test peptides were carried out by stepwise solid-phase methods on *N*-Boc-*p*-(acyloxy)benzhydrylamine–copoly (styrene–1% divinylbenzene). Protected amino acids used were Asp(OBzl) Met(O), and Trp(For). Each synthetic cycle consisted of (i) a 20-min deprotection with 50% CF_3CO_2H–CH_2Cl_2, (ii) neutralization with 5% DIEA/CH_2Cl_2, and (iii) double coupling with preformed symmetrical anhydrides (3 equiv) for 1 h each in CH_2Cl_2 and recoupling in dimethylformamide. Boc-Gly was coupled with DCC alone. All couplings were monitored by the quantitative ninhydrin test.[27]

Pentagastrin Amide. The pentapeptide Boc-Gly-Trp-(For)-Met(O)-Asp(OBzl)-Phe-NH-CHC_6H_5–C_6H_4–$OCOCH_2$ resin was synthesized from N-Boc-*p*-(acyloxy)benzhydrylamine resin (method D; 2 g, 0.80 mmol).

Gradative Deprotection. The pentapeptide resin (0.50 g) was treated with the following protocol: (i) 50% CF_3CO_2H–CH_2Cl_2, 2× (5 min); (ii) CH_2Cl_2, 3× (1 min); (iii) 5% DIEA, 2× (1 min); (iv) CH_2Cl_2, 3× (1 min) (dried in vacuo); (v) HF–DMS–*p*-thiocresol–*p*-cresol (25:65:7.5:2.5, v/v, 10 mL), 1× (120 min), 0°C; (vi) ether–mercaptoethanol (95:5, v/v), 2× (2 min); (vii) CF_3CO_2H–anisole (9:1, v/v), 2× (1 min); (viii) 25% CF_3CO_2H–CH_2Cl_2, 2× (1 min); (ix) CH_2Cl_2, 3× (1 min); (x) 5% DIEA, 2× (1 min); (xi) DMF, 3× (1 min); (xii) 5% NH_2NH_2–DMF (4 mL), 1× (30 min); (xiii) DMF, 1× (1 min) (4 mL). The filtrates of steps xii and xiii, were collected, cooled, and neutralized dropwise with an equivalent amount of glacial acetic acid. In most cases, the peptides precipitated out after dilution with H_2O (20-fold). In such cases, the precipitate was collected, redissolved in 1–10% HOAc, and lyophilized to dryness. Otherwise, the DMF filtrate was reduced to dryness under vacuum to a white powder. The hydrazine salt and peptide were redissolved in the mobile phase containing 0.05% CF_3CO_2H and 5% CH_3OH, and the hydrazine acetate was removed through reversed-phase HPLC. Peptide products were then eluted by the mobile phase containing 80% CH_3OH.

The dried pentapeptide amide was then treated with (xiv) 1% CF_3SO_3H–CF_3CO_2H with 8% *m*-cresol and 2% DMS (2 mL) for 2 h at ambient temperature (or 2% CF_3SO_3H–CF_3CO_2H with 8% *m*-cresol and 2% DMS for 1 h) and (xv) diluted with 10-fold ether, cooled in dry ice bath. If there was no precipitation, pyridine was added (~1%). The precipitate was collected, centrifuged, washed with ether, and dried in vaccuo. It was redissolved and lyophilized in 1–10% HOAc. (Note: step (v) *p*-thiocresol is not necessary if Trp(For) is not present. In such cases, the mixture will be HF–DMS–*p*-cresol (25:65:10, v/v.)

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Formal Steric Enthalpy. Alcohols, Ethers, and Olefins[1,2]

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Formal steric enthalpy (FSE) is a general quantitative measure of the steric properties of a single conformer of a molecule. In this study we develop FSE values for alcohols and ethers and for olefins, providing for the first time a formally defined (though initially unknown) quantitative measure of the steric properties of these key molecules. We have calculated formal steric enthalpies for representative examples. The concept and the procedures may be extended to other classes of compounds.

There has been an accelerating interest in the use of computer techniques based on molecular mechanics for evaluating steric influences on reactions. A serious limitation in such applications has been the lack of a theoretically valid quantitative measure of steric effects. Raw steric energies as derived from molecular mechanics calculations are of limited utility since SE's are force field dependent and have no theoretical significance. Pairwise comparisons of SE values are valid only between isostructural molecules such as conformers and are useless for comparisons among members of general families of molecules.

We have developed a new measure of steric properties that overcomes these limitations for many classes of molecules and have called it formal steric enthalpy (FSE).[3]

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(1) Definitions: SE, steric energy as calculated by molecular mechanics; FSE, formal steric enthalpy as defined in the present study; DETSB, the DeTar–Binzet force field developed in the present study; WHI77, the White 1977 force field.[2]

(2) White, D. N. J.; Bovill, M. J. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1610.

(3) DeTar, D. F.; Binzet, S.; Prashanth, D. *J. Org. Chem., Chem.* **1985**, *50*, 2826.

FSE is an extension of and a refinement of single conformer strain energy.[4-6] In the above reference we presented the underlying concepts and applied them in defining and evaluating FSE's of alkanes.

Rüchardt and his co-workers have made numerous important contributions to the estimation of and the use of strain energies of several types of molecules.[7-10] One advantage of the FSE's over the strain energies is that they can be derived by calculation as well as from enthalpies of formation. They can therefore be defined for molecules that are too ephemeral to study experimentally. A second important advantage is that FSE's provide a general "public" measure of steric properties and thus facilitate comparison of results obtained in different laboratories.

In this study we propose definitions of FSE values for alcohols and ethers and for olefins. We apply the definitions to the calculation of FSE values of representative examples and show that the results provide a consistent account of the steric properties. The methods can readily be extended to other classes of compounds.

Although the formal steric enthalpy of a given conformer may conceptually be considered to be a summation of enthalpy terms arising from distortions of bonds, angles, and torsions plus all intramolecular "nonpolar" nonbonded contributions, the FSE is actually defined operationally in terms of a set of standard molecules and of the formal steric enthalpy values assigned to specified conformers of these standard molecules.

The FSE values are thus defined, but initially unknown, properties of all conformers of a given class of compounds. An estimate of the value for a given conformer may be obtained by applying corrections to the steric energy calculated by molecular mechanics. An estimate may also be derived from thermodynamic data, providing that the data are available for the standard set of molecules as well as the target molecule. An estimate can in principle be obtained by any computational method that provides relative enthalpies of formation. As force fields and other computational methods are improved, all should give convergent estimates of the FSE values.

Equations 1 and 2 show how the FSE may be computed from the steric energy calculated by molecular mechanics. The *d* values of eq 2 are correction terms that serve to remove the residual FBE component from the SE.

$$\mathrm{FSE} = \mathrm{SE} - \mathrm{corrn(ff)} \tag{1}$$

$$\mathrm{corrn(ff)} = d(\mathrm{CH_3})n(\mathrm{CH_3}) + d(\mathrm{CH_2})n(\mathrm{CH_2}) + d(\mathrm{CH})n(\mathrm{CH}) + d(\mathrm{C})n(\mathrm{C}) \tag{2}$$

The FSE value of the conformer of lowest energy may be obtained experimentally from enthalpies of formation by use of eq 3–5. SM is a (small) statistical mechanical correction term that converts the enthalpy of formation of a population of conformers to the enthalpy of formation of the single conformer of lowest energy. The *c* values of eq 4 are group increments whose sum provides the calculated value of the FBE for all conformers of the given molecule.

$$\mathrm{Hf(sngl\ confrmr)} = \mathrm{FBE} + \mathrm{FSE} \tag{3}$$

$$\mathrm{FBE} = c(\mathrm{CH_3})n(\mathrm{CH_3}) + c(\mathrm{CH_2})n(\mathrm{CH_2}) + c(\mathrm{CH})n(\mathrm{CH}) + c(\mathrm{C})n(\mathrm{C}) \tag{4}$$

$$\Delta\mathrm{Hf(sngl\ confrmr)} = \Delta\mathrm{Hf(obsd)} - \mathrm{SM} \tag{5}$$

A fundamental assumption that underlies the definition of FSE values is that the FBE term for any molecule in the set of interest is definable as a summation of group increments, the *c* increments of eq 4 or equivalently the correction terms *d* of eq 2. For this to succeed the FBE contribution for any given structural unit must be independent of the number and of the ordering of all other units in the molecule. The assumption is valid for many types of molecules but would not apply to molecules in which there are, for example, steric effects on resonance. Thus, the definition of FSE values given in eq 1–5 must be applied with care to take into account the limitations.

The procedure for applying eq 1–5 to a given set of molecules involves three steps: identification of the minimum set of structural units necessary for describing the FBE of any member of the given set, selection of suitable standard molecules containing these units, and assignment of a reasonable value of FSE to an appropriate conformer of each standard molecule.[3] For alkanes, four units suffice to define the FBE. These are CH_3, CH_2, CH, and C. We will illustrate the application of this procedure to the definition of FSE values for certain alcohols and ethers and for certain olefins. The procedure is readily generalized to other classes of compounds.

Alcohols and Ethers. For monofunctional alcohols and ethers we find that five additional units suffice to define the FBE component. These are OH, CH_3O, CH_2O, CHO, and CO. The oxygen atoms in the units are to be interpreted as "half" oxygens. Thus, diethyl ether contains two alkyl CH_3 units and two CH_2O units; methyl isopropyl ether contains two alkyl CH_3 units, a CHO unit, and a CH_3O unit. We discern no need for proposing special units for carbons β to the alcohol or the ether oxygen. In the present study we have not treated polyfunctional alcohols or ethers; these may be expected to require additional units such as OCH_2O and will also require appropriate treatment of polar effects.[4]

For defining the *c* group increments and the *d* correction terms we have selected the following standard molecules containing the above units. To the conformer of lowest energy of each we have assigned the arbitrary but reasonable FSE value shown in parentheses: MeOH through *n*-PeOH, *i*-PrOH, *t*-BuOH, MeOEt, MeOPr-*n*, EtOEt (FSE all 0); *s*-BuOH (0.15); MeOPr-*i* (1.00); MeOBu-*t* (2.00); 2-methyl-2-butanol (0.85); *i*-PrOPr-*i* (2.00). The conformers are defined more precisely in Table IV.[11]

The nonzero FSE values assigned to some of the standards are based on estimates of gauche enthalpies. In the earlier paper[3] we have shown that the definition of FSE values of crowded molecules is not very sensitive to choices of the FSE values of the standard molecules as long as the standards are relatively uncrowded. However, it is obvious that absolute consistency in definition is essential if the FSE values for a given class of compounds are to be comparable from one study to the next.

The *c* terms and the *d* terms for the alkoxy units and for OH were evaluated by general least-squares procedures. The resulting values are reported in Table I. We defer for the moment the discussion of errors.

In Table II we summarize the results of applying the increments of Table I to SE data to give FSE values of

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(11) Supplementary material. See paragraph at end of paper.

Table I. Group Increments for Olefins and Alcohols and Ethers

	gp incrnts, c_i (eq 4)	DETSB corrns, d_i (eq 2)	WHI77 corrns, d_i (eq 2)
CH_3	−10.073	0.134	0.249
CH_2	−5.137	0.815	0.109
CH	−2.203	2.272	0.188
C	−0.142	4.855	0.649
CH_3O	−22.138	0.584	
CH_2O	−20.328	0.675	
CHO	−19.129	1.432	
CO	−19.140	3.265	
HO	−25.796	−0.160	
$=CH_2$	6.213		0.097
=CCH	13.690		1.357
=CC2	19.666		2.725
CH_3	−14.935		−1.021
CH_2	−10.000		−0.900
CH	−5.962		−0.027
C	−0.995		−0.521

some 3 dozen conformers of various alcohols and ethers. The statistical mechanical correction is needed only for calculating the experimental FSE values; it corrects the ΔHf value for a population of conformers to the ΔHf value for the conformer of lowest energy. The SM value is not used in estimating FSE values from steric energies since a molecular mechanics calculation provides directly an interpolated or extrapolated estimate for a single conformer. Procedures for estimating SM values have been described earlier.[3] We expect that more extensive investigations of conformers of higher energy will lead to some revisions. We judge that the SM estimates are consistent within about 0.2 kcal/mol.

Alkenes. For alkenes seven additional structural units are needed: $=CH_2$, =CHC, $=CC_2$, α-CH_3, α-CH_2, α-CH, α-C. We provide evidence in the Discussion for the need for the special α increments. These several units suffice for calculating the FBE's olefins having isolated double bonds separated by at least two sp^3 carbons.

Our present treatment of olefins relies entirely on literature data for steric energies[2] except that we have previously made independent calculations of the steric energies for the standard alkanes that are needed to define the *c* and the *d* increments for alkyl groups.[3] Since we have not undertaken an independent investigation of olefins, we are constrained for the present to use the available data in selecting standard compounds and we lack conformational details.

There are 12 potential standard compounds for which both enthalpy data and calculated steric energies are available. These are ethene, propene, 1-butene, 1-pentene, *trans*-2-butene, trans-2-pentene, *trans*-2-hexene, 3-methyl-1-butene, 2-methyl-1-butene, 3,3-dimethyl-1-butene, *trans*-4-methyl-2-pentene, and 2-methyl-1-propene.

It is clear that the several alkene units are not represented to the same numerical extent; to do so rigorously is not possible. The α-C unit is represented only once (in 3,3-dimethyl-1-butene); the $=CC_2$ unit is represented twice (in 2-methylpropene and in 2-methyl-1-butene). The other units are all represented in three or more compounds. The selection of olefin standards may require modification

Table II. Formal Steric Enthalpies of Alcohols and Ethers

					FSE			conform			
	−ΔHf[a]	SM[b]	gauche[c], enth	SE	exptl[d]	calcd[e]	steric[f] crowding				run ID[g]
*methanol[h]	48.08	0.00	0.00	0.38	−0.14	−0.04	−0.04	1			B7AL0111
*ethanol	56.12	0.00	0.00	0.60	0.07	−0.04	−0.04	2			B7AL0211
*1-propanol	61.36	0.09	0.00	1.37	−0.11	−0.09	−0.09	3	A		B7AL0311
2-propanol			0.00	1.80		0.26	0.26	6			B7AL0621
*2-propanol	65.14	0.00	0.00	1.64	−0.06	0.10	0.10	6			B7AL0611
2-butanol			0.70	3.11		0.75	0.05	7	A		B7AL0721
2-butanol			0.70	2.99		0.63	−0.07	7	A		B7AL0711
2-butanol			0.15	2.70		0.34	0.19	7	B		B7AL0741
*2-butanol	69.92	0.25	0.15	2.56	0.03	0.20	0.05	7	B		B7AL0731
*2-methyl-2-propanol	74.72	0.00	0.00	3.59	0.43	0.08	0.08	16			B7AL0811
*1-butanol	65.69	0.33	0.00	2.18	0.45	−0.09	−0.09	A8	A	A	B7AL0411
2-methyl-2-butanol			1.40	5.65		1.32	−0.08	17	A		B7AL0911
*2-methyl-2-butanol	78.86	0.09	0.85	5.27	1.34	0.94	0.09	17	B		B7AL0931
*1-pentanol	71.47	0.56	0.00	3.00	−0.42	−0.09	−0.09	AG	A	A	B7AL0511
2,3,3-trimethyl-2-butanol			3.10	13.40		4.77	1.67	19			BN7D14AL
2,3,4-trimethyl-3-pentanol			5.75	16.50		8.18	2.43	23	D		BN7D01AL
3-ethyl-3-pentanol			4.35	11.44		5.48	1.13	26	E		BIN7AL10
2,2,4-trimethyl-3-pentanol			3.95	14.62		5.55	1.60	14	A		BN7D06AL
2-methyl-3-ethyl-3-pentanol			5.20	15.00		7.45	2.25	27	N		BN7D02AL
2,2,3,4-tetramethyl-3-pentanol			6.60	22.70		11.66	5.06	24	C		BN7D09AL
2,2-dimethyl-3-ethyl-3-pentanol			6.05	20.74		10.48	4.43	28	F		BN7D10AL
2,4-dimethyl-3-ethyl-3-pentanol			7.85	19.54		10.40	2.55	29	J		BN7D04AL
2,4-dimethyl-3-isopropyl-3-pentanol			8.70	24.26		13.53	4.83	32	C		BN7D05AL
*ethyl methyl ether	51.73	0.27	0.00	1.50	0.53	0.10	0.10	2	1	A	B7ET0121
ethyl methyl ether			1.00	2.35		0.95	−0.05	2	1	B	B7ET0111
*diethyl ether	60.27	0.73	0.00	1.68	−0.19	0.06	0.06	2	2	AA	B7ET0221
diethyl ether			1.00	2.54		0.92	−0.08	2	2	AB	B7ET0211
**n*-propyl methyl ether	56.82	0.96	0.00	2.26	−0.10	0.05	0.05	3	1A	A	B7ET0321
n-propyl methyl ether			1.00	3.14		0.93	−0.07	3	1A	B	B7ET0311
isopropyl methyl ether			2.00	3.91		1.62	−0.38	6	1	A	B7ET0431
*isopropyl methyl ether	60.24	0.09	1.00	3.34	1.08	1.05	0.05	6	1	B	B7ET0411
isopropyl methyl ether			1.00	3.34		1.05	0.05	6	1	B	B7ET0421
**tert*-butyl methyl ether	69.85	0.00	2.00	6.06	1.64	1.80	−0.20	16	1		B7ET0611
diisopropyl ether			6.50	9.77		6.37	−0.13	6	6	AA	B7ET0541
diisopropyl ether			4.25	7.90		4.50	0.25	6	6	AB	B7ET0521
*diisopropyl ether	76.20	0.29	2.00	5.28	2.06	1.88	−0.12	6	6	BB	B7ET0511

[a] From refs 12 and 13. [b] To correct ΔHf observed to ΔHf of single conformer. [c] See text. [d] From Hf. [e] From SE. [f] Calculated FSE–gauche enthalpy. [g] Keys to Table IV.[11] [h] Asterisks refer to standard compounds for deriving *c* values and *d* values (eq 1–5).

when the olefins are subjected to more detailed studies.

Although *c* and *d* increments can be computed from a minimal set of standard compounds, it is desirable to use an enlarged set in order to provide a check of internal consistency. Redundancy is particularly advisable for establishing the formal bond enthalpy increments based on enthalpies of formation. The difficulties of achieving the required experimental accuracy of enthalpies of formation are great, and the scatter of experimental FSE's may be expected to be larger than the scatter of calculated FSE's. We have therefore included three additional compounds in the standard set used with the ΔHf data. These aree 1-hexene, *trans*-3-hexene, and 3-methyl-1-pentene.

We have assigned FSE = 0 to the conformer of lowest energy of each compound of the standard set except for 2-methyl-1-butene for which we have used 0.4 and 3,3-dimethyl-1-butene for which we have used FSE = 1.0. The several FSE assignments are tentative; several deserve a more detailed investigation, particularly the latter two and those for 3-methyl-1-butene and for *trans*-4-methyl-2-pentene.

It is clear that the definition of FSE's that we propose for olefins is based on a specialized definition of "strain". In the conventional terminology the double bond of ethylene and other olefins is considered to be strained. We do not disagree with that concept but find it more useful to segregate the double-bond strain common to all olefins by incorporating it into the FBE term. The FSE strain of olefins is then limited to the added steric effects, owing to intramolecular interaction of the substituent groups.

We derived the *c* and the *d* values by an overall least-squares procedure for these sets. Since the seven group increments are correlated, we have chosen to stabilize the definitions by assigning a fixed value to the α-CH_2 unit. This unit has been chosen since it occurs in many compounds. The group increment values obtained for the olefin units are presented in Table I. We defer discussion of the errors.

The formal steric enthalpies of some 50 olefins are presented in Table III. The statistical mechanical estimates are based primarily on analogy with calculated SM values for alkanes and unpublished SM values for esters. Errors in these values will lead to corresponding errors in the experimental FSE values. We believe that these estimates are correct to within better than 0.3 kcal/mol. For present purposes we have relied on the thermodynamic data reported in the collections by Stull et al.[12] and by Cox and Pilcher.[13] There are a few inconsistencies in the thermodynamic data, and these result in some scatter in the derived experimental FSE values. The formal bond enthalpy increments for the experimental FSE's were derived from the Stull et al. data.

Discussion. We apply several criteria to evaluate the suitability of the choices of standard units for alcohols and ethers and for olefins. The first is consistency; the structural units and the standard compounds chosen to define the formal bond enthalpy must provide *c* values and *d* values having the minimum property of reproducing the assigned formal steric enthalpies of the standard molecules. This can be judged in terms of the standard deviations of the calculated FSE values in comparison with the assigned FSE values.

A second criterion is based on a comparison of the FSE's with expected values. One possiblity is to compare FSE's with estimated gauche enthalpies. A more qualitative comparison may also be useful; the FSE's should increase in a sensible progression as structures become more crowded.

That the group increments derived for the alcohols and ethers (Table I) do meet the first criterion of consistency is shown by the standard deviations of the FSE's calculated for the standard compounds identified by asterisks in Table II, as compared with the assigned FSE values. The assigned values are those in the column labeled gauche enthalpy. The *c* values yield experimental FSE's (derived form enthalpies of formation) that reproduce the assigned FSE's with a standard deviation of 0.36 kcal/mol and with a correlation coefficient squared of 0.75. The standard deviation is well within the probable limits of accuracy of the thermodynamic data. The correlation coefficient is small because the standards have a small range of FSE values.

The *d* values yield calculated FSE's from the steric energies derived by molecular mechanics that agree with the assigned FSE's within a standard deviation of 0.12 kcal/mol; the square of the correlation coefficient is 0.974. We conclude that the criterion of consistency has been met.

To apply the second criterion we have developed incremental estimates of gauche enthalpy. In the earlier paper[3] we have discussed the rationale for formally selecting FSE values of 0.7 kcal/mol to isoalkanes (one gauche interaction) and 1.4 kcal/mol to neoalkanes (two gauche interactions). We also showed that the overall results are not strongly sensitive to the selected values.

Oxygen-containing compounds involve both a sequence containing an external oxygen as in CCCO and a sequence containing an internal oxygen as in CCOC. Most of the gauche enthalpy for alkanes is due to interactions between atoms on the terminal carbon atoms, and since a terminal oxygen atom has only one attached atom and that atom can be rotated out of the way, the interaction will be smaller for CCCO than for CCCC. On the other hand a CO bond is shorter than a CC bond and the interaction between terminal carbons will be higher for CCOC than for CCCC.

The gauche value of 1.00 we have used for CCOC is based on an analysis of steric energies of conformers of methyl ethyl ether, of methyl *n*-propyl ether, and of diethyl ether. It is rather smaller than the estimate of 2.1 obtained by Jorgensen[14] using STO-3G optimized geometries for ethyl methyl ether. It is also smaller than the "experimental" value of 1.5 derived from infrared studies on ethyl methyl ether.[15] The higher gauche values are less consistent with the experimental FSE values for diisopropyl ether (2.06) and of *tert*-butyl methyl ether (1.64). While these experimental values are in reasonable agreement with the estimates based on the 1.0 gauche enthalpy, which predicts 2.0 for both, they are not consistent with the higher gauche values. These predict FSE values of 4.2 and of 3.0, respectively, for both ethers. Benson has analyzed gauche energies for several types of molecules.[16]

Gauche estimates are based on a count of gauche interactions of the following types: for each gauche CCCC, 0.70; for each gauche OCCC, 0.15; for each gauche CCOC, 1.00. For each g^+g^- sequence we add a further increment of 1.25 for CCCCC or for CCCOC and a further increment of 1.00 for CCCCO and for CCOCC. Application of these rules yields the estimated formal gauche enthalpy values

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Table III. Formal Steric Enthalpies of Alkenes

	ΔHf				exptl FSE		
alkene	Stull[a]	Cox[b]	SM[c]	SE[d]	Stull[e]	Cox[f]	FSE[g] WHI77
*ethylene[j]	12.50	12.45	0.00	0.11	0.07	0.02	−0.08
*propene	4.88	4.88	0.00	0.44	−0.09	−0.09	0.01
*1-butene	−0.03	−0.20	0.00	0.80	0.14	−0.03	0.00
*1-pentene	−5.00	−5.33	0.06	1.02	0.25	−0.08	0.11
*1-hexene	−9.96	−9.95	0.29		0.19	0.20	
1-heptene	−14.89	−14.81	0.52		0.17	0.25	
1-octene	−19.82	−19.41	0.75		0.15	0.56	
5-methyl-1-hexene		−15.70	0.15			1.73	
*3-methyl-1-butene	−6.92	−6.61	0.05	1.98	−0.77	−0.46	0.06
*3-methyl-1-pentene	−10.76		0.38		0.20		
4-methyl-1-pentene	−10.54		0.22		1.69		
*3,3-dimethyl-1-butene[h]	−10.31		0.00	2.68	1.00		1.00
4,4-dimethyl-1-pentene		−19.44	0.00	2.16		1.02	0.21
**trans*-2-butene	−2.67	−2.99	0.00	0.68	−0.18	−0.50	0.01
**trans*-2-pentene	−7.59	−7.93	0.00	0.98	0.04	−0.30	−0.06
**trans*-2-hexene	−12.88	−12.88	0.06	1.18	−0.18	−0.18	0.03
**trans*-3-hexene	−13.01	−13.01	0.00		−0.24	−0.24	
**trans*-4-methyl-2-pentene	−12.99		0.00	2.11	0.67		−0.05
trans-4,4-dimethyl-2-pentene		−21.22	0.00			−2.45	
trans-2,2-dimethyl-3-hexene		−25.73	0.00			−1.82	
1,5-hexadiene			0.00	1.29			0.18
cis-2-butene	−1.67	−1.86	0.00	1.99	0.82	0.63	1.32
cis-2-pentene	−6.71	−7.00	0.00	2.23	0.92	0.63	1.19
cis-2-hexene	−12.51	−12.51	0.06	2.40	0.20	0.20	1.25
cis-3-hexene	−11.38	−11.38	0.00		1.39	1.39	
cis-4-methyl-2-pentene	−12.03		0.00	2.60	1.63		0.44
cis-4,4-dimethyl-2-pentene		−17.36	0.00			1.41	
cis-2,2-dimethyl-3-hexene		−21.34	0.00			2.57	
*2-methyl-1-propene	−4.04	−4.26	0.00	0.85	−0.05	−0.27	0.07
*2-methyl-1-butene[i]	−8.68	−8.55	0.00	1.48	0.45	0.58	0.33
2-ethyl-1-butene	−12.32				7.83		
3-ethyl-2-methyl-1-pentene		−23.97	0.00			1.47	
2,3,3-trimethyl-1-butene		−20.53	0.00			−0.26	
2,4,4-trimethyl-1-pentene		−26.55	0.00	3.43		2.87	1.13
2-methyl-2-butene	−10.17	−10.12	0.00	2.53	1.28	1.33	1.51
2-methyl-2-pentene	−14.28		0.00	2.66	2.31		1.27
(*Z*)-3-methyl-2-pentene	−13.80		0.00		2.79		
(*E*)-3-methyl-2-pentene	−14.02		0.00	2.67	2.57		1.28
(*Z*)-3-methyl-3-hexene		−18.98	0.00			2.75	
(*E*)-3-methyl-3-hexene		−18.36	0.00			3.37	
2,4-dimethyl-2-pentene		−21.20	0.00			1.42	
2,4,4-trimethyl-2-pentene		−25.07	0.00			2.66	
2,3-dimethyl-2-butene	−14.15		0.00	4.91	6.26		3.54
2-methyl-1-pentene	−12.49		0.06		1.72		
cyclopentane	−18.46	−18.44	0.00		7.23	7.25	
cyclopentene	7.87	8.23	0.00	7.70	5.63	5.99	6.68
methylcyclopentane	−25.50	−25.25	0.00	8.13	7.32	7.57	7.26
1-methylcyclopentene	−1.30	−0.60	0.00	7.76	5.42	6.12	6.39
3-methylcyclopentene	2.07	2.00	0.00	7.81	5.86	5.79	5.67
cyclohexane[j]	−29.43	−29.50	0.00	3.45	1.39	1.32	2.80
methylcyclohexane	−36.99	−36.98	0.00	3.47	0.97	0.98	2.49
cyclohexene	−1.28	−1.08	0.00	2.78	1.61	1.81	1.65
1-methylcyclohexene		−10.34	0.00	2.84		1.51	1.36

[a] Reference 12. [b] Reference 13. [c] Statistical mechanical correction. See text. [d] Steric energy from ref 2. [e] From Stull ΔHf eq 3–5; group increments from Table I. [f] From Cox ΔHf eq 3–5. [g] From WHI77 SE's (2) using eq 1 and 2 with group increments from Table I. [h] FSE assigned as 1.00. [i] FSE assigned as 0.40. [j] Expected gauche enthalpy is 3(0.7) or 2.1. There are three gauche interactions in cyclohexane. Asterisks refer to compounds used in calculating *c* and *d* values.

listed in Table II. For the standard conformers the assigned FSE is equal to the formal gauche enthalpy.

For molecules that are not too crowded, the formal gauche enthalpy should be nearly equal to the FSE. The difference, FSE − gauche enthalpy, is reported in the column labeled steric crowding. There is good agreement for 25 examples. The 11 compounds that show appreciable crowding are all expected to have considerable steric congestion. Qualitatively and quantitatively, therefore, the FSE values of alcohols and ethers meet the third criterion.

The alcohols in Table II were selected on two different criteria. For those marked with an asterisk we examined a sufficient number of conformers to ascertain the range of FSE values and to locate the global minima. Three pairs show the small energy difference due to an endo vs. an exo interaction of the hydrogen atom on oxygen with alkyl groups. These are 2-propanol and the 7A pair and the 7B pair of 2-butanol. The difference between these latter two pairs is that the 7B conformer has an s-trans chain.

The more highly substituted alcohols were chosen in the initial stages of a project, which will, among other considerations, provide a comparison of steric effects of R groups in a series of alcohols ROH with their effects in esters RCOOMe. On the basis of extensive (unpublished) ester calculations, we judge that some of these represent global minima while others do not.

More detailed information about the conformations is presented in Table IV.[11] Since these compounds all have several local minima, it is necessary to exercise care in making comparisons of FSE's.

Turning now to olefins, we apply the first criterion and find that the standard deviation of the experimental FSE values of the standard compounds in comparison with the assigned FSE's is 0.4 while the standard deviation of the FSE's calculated from the White and Bovill SE's is 0.07. Both values are quite acceptable. The correlation coefficients are low since all but two assigned FSE's are 0.

Applying the second criterion, we compare the FSE's derived from enthalpies of formation with those calculated from the Bovill and White steric energies. For 23 acyclic and cyclic olefins of the Stull set, the standard deviation is 0.96 and the square of the correlation coefficient is 0.80; for the 20 olefins of the somewhat different Cox set, the standard deviation is 0.70 and the square of the correlation coefficient is 0.89. These standard deviations are somewhat larger than we would like and may indicate limitations of the force field. We note, however, that there also are rather large inconsistencies in the experimental data.

We have a definitive answer to the question of the need for the special α units for CH_3, CH_2, CH, and C groups adjacent to an sp^2 carbon atom. Unless we use these special units, the correlations are poor. Thus, if we base the definition of FBE values on only seven structural units, viz, the four alkyl groups plus the three olefin units $=CH_2$, $=CCH$, and CC_2, then the best set of *c* and of *d* values that can be obtained leads to a much poorer consistency. The standard deviation for the calculated FSE values is increased from 0.08 up to 0.4 and for the experimental FSE values is increased from 0.4 to 1.2.

There is a rationale for the need for these special α units. With respect to steric energies, the steric environment of a CH_2 group in $C^3CH_2C^3$ is different than in $C^3CH_2C^2$, and this needs to be corrected appropriately.

These considerations lead to the expectation that additional units will be needed for such sequences as $C^2CH_2C^2$. The present treatment applies, therefore, only to compounds with double bonds isolated by at least two sp^3 carbon atoms. We predict that several additional units will have to be introduced such as double α CH_2, CH, and C units for compounds having pairs of double bonds isolated by just one sp^3 carbon. The resonance possibilities for conjugated systems introduces contributions to the formal bonding enthalpy that are no longer adequately approximated by the additivity treatment. Further units may be needed to treat molecules containing oxygen in addition to unsaturation. Allinger has addressed the calculation of steric energies of many types of olefins.[4]

It is instructive to consider the data for two of the series of alkenes in Table III. For the *cis*-alkenes the formalism requires that *cis*-2-butene, *cis*-2-pentene, *cis*-2-hexene, and *cis*-3-hexene should all have the same value of FSE. For the Stull et al. data, the average is 0.83 and the standard deviation of the average is 0.24. For the White data, on three of these the average is 1.25 and the standard deviation of the average is 0.04. This difference may reflect limitations of the force field.

The second set is a series of 1-alkenes from propene through 1-octene. All should have FSE = 0. The Cox and Pilcher data (not used in the calibration) give the reasonable value of 0.14, and the standard deviation of the average is 0.10. For 1-alkenes with remote methyl substituents the FSE's should be the same as for the corresponding alkanes. On this basis the FSE values for 4-methyl-1-pentene and for 5-methyl-1-hexene should both be 0.7. If there is an additional steric interaction with the double bond, then the FSE for 4-methyl-1-pentene will be larger than the 0.7 value predicted. The respective experimental FSE's are 1.69 and 1.73, which may be out of line.

The DeTar–Binzet Force Field. The alkane part of this force field (DETSB) has been described briefly in an earlier paper.[3] In the supplementary material (Table V)[11] we provide the detailed values, including those for the oxygen sequences, used in the present study.

The DETSB force field uses only five types of atoms: H11, C21 (sp^3), C29 (sp^2), 038 (sp^3), 039 (sp^2). This set is also used in studies of esters, to be reported elsewhere. Even this limited set of atoms can be assembled into well over 100 types of bonds, angles, torsions, and nonbonded interactions. Thus, these five types of atoms define eight chemically possible types of bonds of which six have been implemented; types 038–038 (peroxide) and C29–H11 (olefin, aldehyde) have not been used in our studies. There are 26 possible types of angles of which we have used 15. The unused types include various peroxides, anhydrides, and α-hydroxy acids. The five atoms potentially define 55 types of torsions of which 21 have been used. Of the 15 possible nonbonded interactions we have used eight. Some 80 constants had therefore to be selected in order to define the combinations used, including cubic corrections for selected angles but using only one type of barrier for each torsion.

Except for the nonbonded Lennard–Jones constants, which were adjusted by a least-squares procedure, the rest of the constants have been borrowed or assigned by analogy, and in some cases hindsight would suggest better choices.

All calculations were performed with the program MOLMEC and related programs. On the basis of replicate calculations starting from different geometries, we find that SE values are usually reproduced to 0.01 kcal/mol. Occasional replicate calculations differ by a few hundredths. Some of the data in Table II were obtained with a variant force field that omitted some torsion barriers. We have made appropriate minor corrections to the FSE values for this omission and on the basis of test recalculations judge that they are comparable to data that would be obtained on recalculation to within 0.2 kcal/mol.

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Supplementary Material Available: Table IV (formal steric enthalpies of alcohols [methanol, ethanol, propanols, butanols, pentanols; includes various methyl-substituted derivatives] and of ethers [7]) and Table V (bond distances and bond angles used in the DETSB force field) (8 pages). Ordering information is given on any current masthead page.