Thermodynamic Functions of Conformational Changes. 2. Conformational Entropy as a Measure of Information Accumulation

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Various folded molecular structures contain different amount of information. The relative amount of information may be related to relative entropy or entropy change. The conformational entropy change for *n*-butane has been computed as the function of rotation around the central C−C bond. It appears that the g^+ or g^- conformers contain about 16% more information than the anti-structure. Furthermore, the syn conformation with the two groups eclipsed contained about 42% more information than the fully staggered anti orientation. The conformational entropy function calculated from 3*N* − 7 internal degrees of freedom was found to be a continuous function.

Introduction

The computation of the entropy change along the reaction coordinate associated with the conformational folding is of primary importance. Since the increase of the information is measured by entropy lowering, the folded conformation is expected to contain a considerable amount of information. As the entropy lowering of the folding process diagnostically measures the increase of information incorporated in the molecular system during folding, the purpose of the present paper is to study the conformational process within one of the simplest molecules: *n*-butane.

Butane conformations have often been analyzed over the years using both experimental and theoretical means.[1−12] In most organic chemistry textbooks, conformational analysis is presented in terms of conformational potential energy (Δ*E*) curves (PEC) and sometime in terms of conformational potential enthalpy (Δ*H*) curves. However, conformational stability is expressed rigorously with relative Gibbs Free Energy (Δ*G*) values that take into account the entropy contribution (Δ*S*), according to (1).

$$\Delta G = \Delta H - \mathrm{T}\Delta S \tag{1}$$

In the case of *n*-butane, the relative stability of the gauche conformer with respect to the anti conformer is given by (2):

$$\Delta G[a \rightarrow g] = \Delta G[g] - \Delta G[a] \tag{2}$$

which incorporates the corresponding entropy contribution, however small that value may be.

$$\Delta G[a \rightarrow g] = \Delta H[a \rightarrow g] - \mathrm{T}\Delta S[a \rightarrow g] \tag{3}$$

Methods

We wish to report the variation of entropy as a function of rotation about the central carbon−carbon bond of *n*-butane, defined by the C−C−C−C dihedral angle. The complete basis set method (CBS4[13,14]) contains HF/3-21G*geometry optimization and frequency calculation. To obtain the effect of electron correlation on geometry, gradient optimization and frequency calculations were carried out at the MP2/6-311G(d,p) level of theory. The question "under what condition is the entropy of a conformational change a continuous function" needs to be addressed. The entropy computed is dominated by the contribution of the vibrational frequencies as outlined in Scheme 1. Frequencies in turn are computed from the second derivatives of the conformational energy. As illustrated in Figure 1, it is in the nature of the conformational potential energy functions that

SCHEME 1. Protocol Used for Entropy Calculation Based on Gaussian Computations

Contribution from translation:

$$S_t = R(\ln(q_t e) + T\left(\frac{3}{2T}\right)) = R(\ln q_t + 1 + \frac{3}{2})$$

where:

$$q_t = \left(\frac{2\pi m k_B T}{h^2}\right)^{3/2} \frac{k_B T}{P}$$

Contribution from rotation

$$S_r = R(\ln q_r + T\left(\frac{(\partial \ln q_r)}{\partial T}\right)_V) = R(\ln q_r + \frac{3}{2})$$

where:

$$q_r = \frac{\pi^{1/2}}{\sigma_r}\left(\frac{T^{3/2}}{(\Theta_{r,x}\Theta_{r,y}\Theta_{r,z})^{1/2}}\right)$$

Contribution from vibrational motion:

$$S_v = R(\ln q_v + T\left(\frac{(\partial \ln q)}{\partial T}\right)_V) = R(\ln q_v + T\left(\sum_K \frac{\Theta_{v,K}}{2T^2} + \sum_K \frac{(\Theta_{v,K}/T^2)e^{-\Theta_{v,K}/T}}{1-e^{-\Theta_{v,K}/T}}\right))$$

$$= R\left(\sum_K \frac{\Theta_{v,K}}{2T} + \ln(1-e^{-\Theta_{v,K}/T}) + T\left(\sum_K \frac{\Theta_{v,K}}{2T^2} + \sum_K \frac{(\Theta_{v,K}/T^2)e^{-\Theta_{v,K}/T}}{1-e^{-\Theta_{v,K}/T}}\right)\right)$$

$$= R\left(\sum_K \ln(1-e^{-\Theta_{v,K}/T}) + \left(\sum_K \frac{(\Theta_{v,K}/T)e^{-\Theta_{v,K}/T}}{1-e^{-\Theta_{v,K}/T}}\right)\right)$$

$$= R\sum_K \left(\frac{(\Theta_{v,K}/T)}{e^{\Theta_{v,K}/T}-1} - \ln(1-e^{-\Theta_{v,K}/T})\right)$$

Total entropy for the electronic ground state:

For the electronic ground state the total molecular entropy is the sum of the above three components.

$$S_{total} = S_t + S_r + S_v$$

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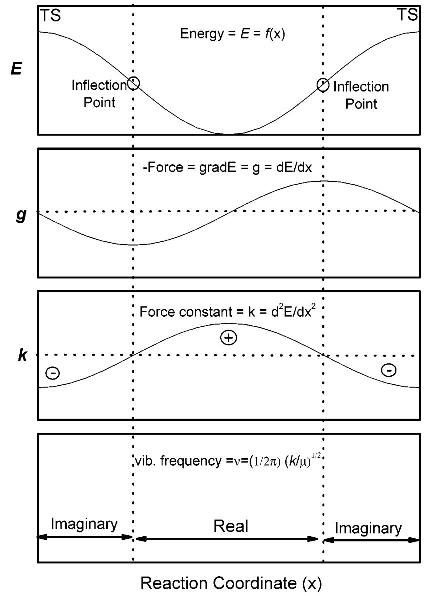

Figure 1. Mathematical characteristics of an idealized potential energy curve (top), its first derivative (g), its second derivative (k), and its real and imaginary domains (bottom) of the vibrational frequency associated with the reaction coordinate.

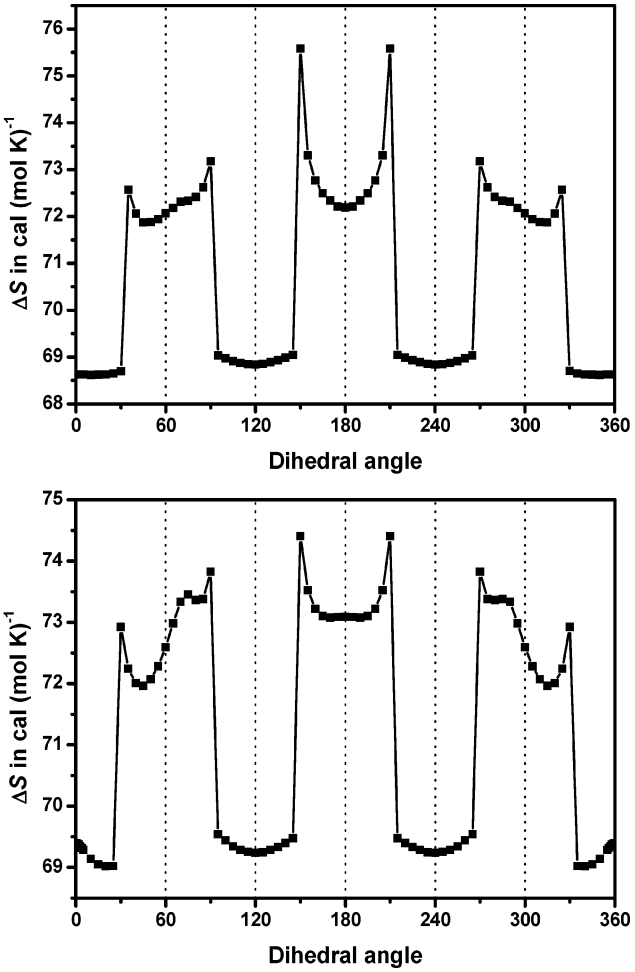

Figure 2. Discontinuity of entropy of butane as a function of rotation about the central C−C bond, computed at the CBS4 (upper panel) and MP2/6-311G** (lower panel) level of theories.

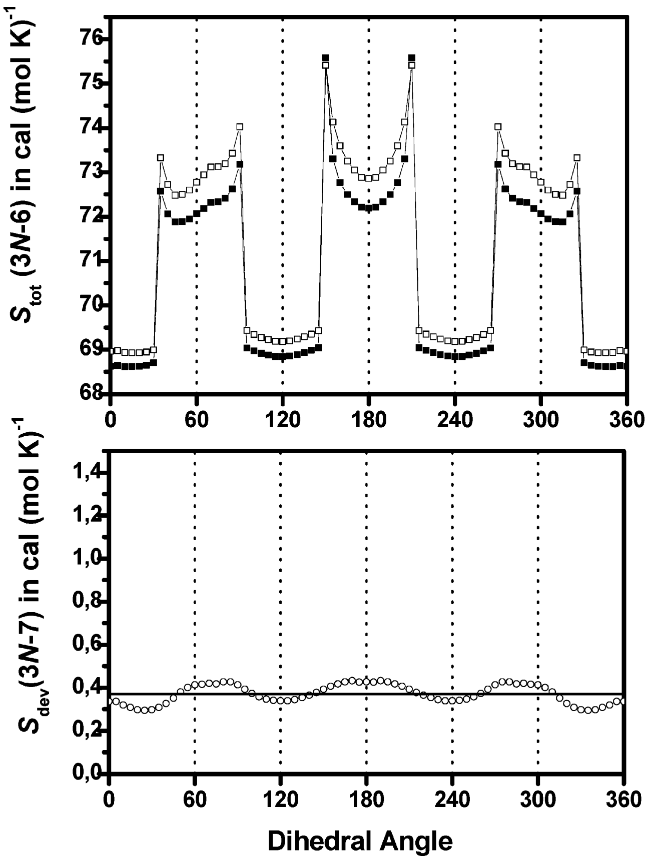

Figure 3. Total entropy (upper panel) calculated with harmonic oscillator (solid squares) and hindered rotor approximation (open squares). Difference (lower panel) of the two methods plotted for $3N - 7$ internal degrees of freedom with an average of 0.37 ± 0.04 cal (mol K)$^{-1}$.

the vibrational frequency associated with the reaction coordinate is real at the minimum energy point and its vicinity. This is valid for as long as the curvature, i.e., the second derivative of the potential energy function, is positive (within the two nearest inflection points of the potential energy function). Consequently, entropy is defined only in this range but not in the regions of the adjacent transition states (TS), because there the vibrational frequency associated with the reaction coordinate is imaginary. This has been recognized earlier by Eyring[15] and Polanyi[16] in connection with formulation of the absolute rate theory. Figure 2 shows that if all $3N - 6$ internal coordinates are included (including the reaction coordinate) in the calculation of entropy, the resulting entropy will be a discontinuous function of the rotational coordinate. Thus, normal coordinate analyses were carried out for all internal coordinates, which were at their minima, except the internal rotation about the central C−C bond. To construct the continuous thermodynamic functions about the rotation of the central C−C bond, the dihedral angle was varied in 5-deg steps. To calculate the vibrational contributions to the thermodynamic functions, the harmonic oscillator approximation is frequently used. For low frequency modes this approximation frequently breaks down, but such internal rotation can be readily treated as a hindered rotor. Using this model for the two $-CH_3$ rotors of the butane, contribution of the hindered rotor approximation to the $3N - 7$ entropy function is a nearly constant term of 0.37 ± 0.04 cal (mol K)$^{-1}$ as shown in Figure 3. For this reason, the use of harmonic approximation leads to a relatively small error for the methyl rotation in butane. The lowest frequency associated with the rotation of the central C−C bond was omitted from the calculations since it becomes imaginary at the transition states. Clearly, it was necessary to neglect the internal coordinate of rotational motions about the central C−C bond along the whole reaction path, which is

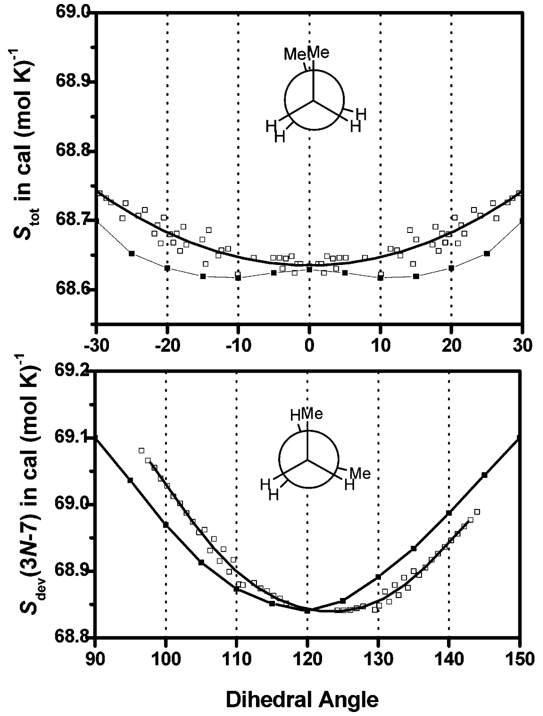

Figure 4. Comparison of entropy values computed with projected frequency calculations along IRC path (open squares) and entropies calculated for $3N - 7$ degrees of freedom (solid squares): upper panel, vicinity of fully eclipsed conformation (syn); lower panel, vicinity of partially eclipsed conformation (120°).

TABLE 1: Enthalpies and Gibbs Free Energies for Various Conformations of *n*-Butane Computed at CBS4 Level of Theory, Where the Literature Values Are Also Shown for Comparison

$\Delta[x - a]$	$3N - 6^a$	$3N - 7^b$	lit.
ΔH_{gauche}	0.696		0.6[24] 0.59[25]
$\Delta H^{\ddagger}_{120°}$	2.99	3.60	3.31[25]
$\Delta H^{\ddagger}_{0°}$	5.44	6.05	5.44[25]
ΔG_{gauche}	0.701		
$\Delta G^{\ddagger}_{120°}$	3.77	4.04	
$\Delta G^{\ddagger}_{0°}$	6.29	6.56	

[a] ($3N - 6$) and ($3N - 7$) degrees of freedom for minima and saddle point, respectively. [b] ($3N - 7$) degrees of freedom for both minima and saddle points.

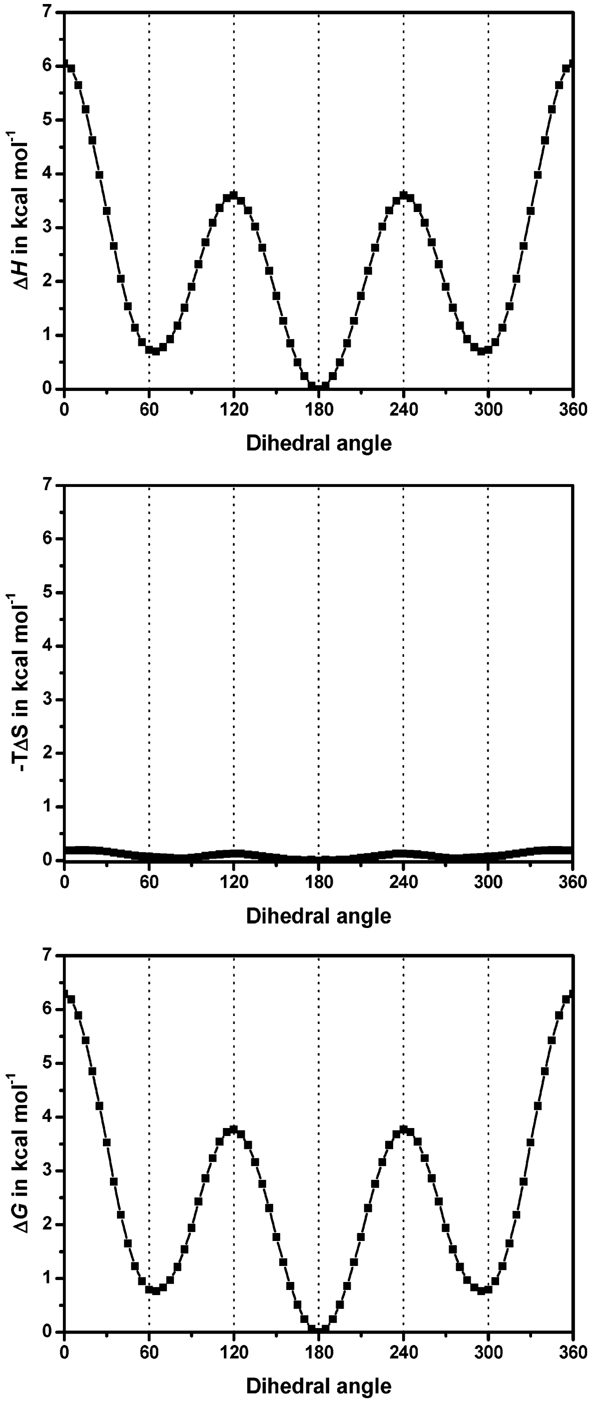

Figure 5. Thermodynamic functions (ΔH, $-T\Delta S$, and ΔG) computed at the CBS4 level of theory.

similar to the analysis of saddle point geometry in the transition state theory.[15,16] Consequently, the present thermodynamic functions (ΔH, ΔG, and S) contain $3N - 7$ internal degrees of freedom. Also, no symmetry contribution to the entropy was applied. It is not trivial to define the thermodynamic functions for nonstationary points. The corresponding degree of freedom must be removed, preferably by projection, rather than just dropping a normal mode instead of doing a statistical average in the direction of the nonzero force. The entropy changes of *n*-butane along the reaction coordinate obtained by classical frequency calculations while neglecting the reaction coordinate, and projected frequency calculations are compared in Figure 4. The projected frequencies were calculated for all optimized geometries along the reaction path. Both curves were continuous and gave similar patterns near the dihedrals along which projected calculations were made. Unfortunately, the results of the projected frequency analysis are very much dependent on the accuracy of the optimized geometries.[17] Although very tight optimization criteria were set for each of the points of the projected calculations, small deviations from the ideal continuous curve still exist. When using classical frequency analysis, tight optimization is enough to obtain a continuous entropy curve without any deviating points. All computations were carried out with the Gaussian-03 program package[18] under tight optimization options.

Results and Discussion

Table 1 lists the relative enthalpies (ΔH and $\Delta H^{\ddagger}$) and the Gibbs free energy (ΔG and $\Delta G^{\ddagger}$) values. Figure 5 shows the potential enthalpy, potential free energy as well as the entropy contribution ($-T\Delta S$) as a function of the central dihedral angle of *n*-butane. The corresponding entropies (ΔS and $\Delta S^{\ddagger}$) are listed in Table 2.

TABLE 2: Entropy and Associated Entropy Change Values [cal (mol K)$^{-1}$] of Various Conformations of *n*-butane Computed at the CBS4 and MP2/6-311G(d,p) [in Parentheses] Levels of Theory, Where the Experimentally Determined Values Are Shown for Comparison

	structure	S^a	ΔS	$T\Delta S$ (cal mol^{-1})	$-\Delta S/R$	ref
computed	*a*	72.189	0.000	0.000	0.000	this work
		[73.092]	[0.000]	[0.000]	[0.000]	
	g	72.181	−0.008	−2.385	0.004	
		[72.594]	[−0.498]	[−148.479]	[0.251]	
	s^0 or $\ddagger_{0°}$	69.019	−3.17	−945.136	1.595	
		[69.540]	[−3.552]	[−1059.029]	[1.788]	
	$s^+ = s^-$ or $\ddagger_{120°}$	68.840	−3.349	−998.504	1.685	
		[69.240]	[−3.852]	[−1148.474]	[1.939]	
expt		71.99				26
expt		72.06				27

[a] Previously calculated values: 73.643 and 72.253 cal (mol K)$^{-1}$ for *a* and *g* conformers, respectively.[6]

In observing the functional change of entropy (*S*) and its components, it is easy to notice that the largest component of *S* originates from translation (about 55% of the total change) and is invariant to the torsion about the central carbon−carbon single bond. The component originating from rotation (about 35% of the total) shown in Figure 6 varies only very slightly with the C−C−C−C dihedral angle. In contrast, vibrations that have the smallest contribution (about 10% of the total) predetermine the shape of the function. The function shown at the top of Figure 6 may be referred to as the conformational potential entropy curve.

Of all the vibrational modes, the lowest frequency (No. 1) associated with the C2−C3 torsion is neglected, as it becomes imaginary at the transition state and in the vicinity of it. The next four lowest vibrational frequencies (Nos. 2, 3, 4, and 5) dominate the overall shape of the function of the entropy as illustrated in the lower part of Figure 6. Frequencies No. 2 and 5 are the symmetric and asymmetric Me-C−C and C−C-Me bond angle vibrational modes. Frequencies No. 3 and 4 are responsible for the conrotatory and disrotatory motions of the two methyl groups. Their maximum rotation angles of 60 and 90° appear to be responsible for the shape of the total entropy in the 40−80° range.

From Figure 7, we can see that the staggered conformations have the following inequality at both levels of theory applied:

$$S[a] > S[g^+] = S[g^-] \tag{4}$$

and the relationship for the eclipsed conformation is analogous for the S[min] values in the vicinity of S[s^+] and S[s^-]

$$S[s^0] < S[s^+] = S[s^-] \tag{5}$$

It should perhaps be emphasized that both ΔH and ΔG as a function of rotation about the central C−C bond exhibit 3 minima and 3 maxima (Figure 5). In contrast, ΔS as a function of the same dihedral angle (C_1−C_2−C_3−C_4) exhibits 4 minima and 4 maxima in the 0−360° range. It is particularly interesting that the minimum entropy, which is expected to be at 0° (s^0 or syn conformation), is not the global minimum but a local maximum. The global entropy minimum occurs in the vicinity of that local maximum within 20° in both the positive (+20°) and the negative (−20°) direction. Obviously, the minimum was split to two minima with a TS between them; an extra minimum and an extra maximum appeared as was supposed to happen in the case of periodic functions.[19,20] Nevertheless, it is clear that there is a decrease in entropy as we progress from the anti, or fully extended conformation, to the syn^0, or fully folded conformation. This decrease is not monotonic since it goes though minima and maxima. Such negative ΔS suggests that there is a reduction in disorder during the folding process.

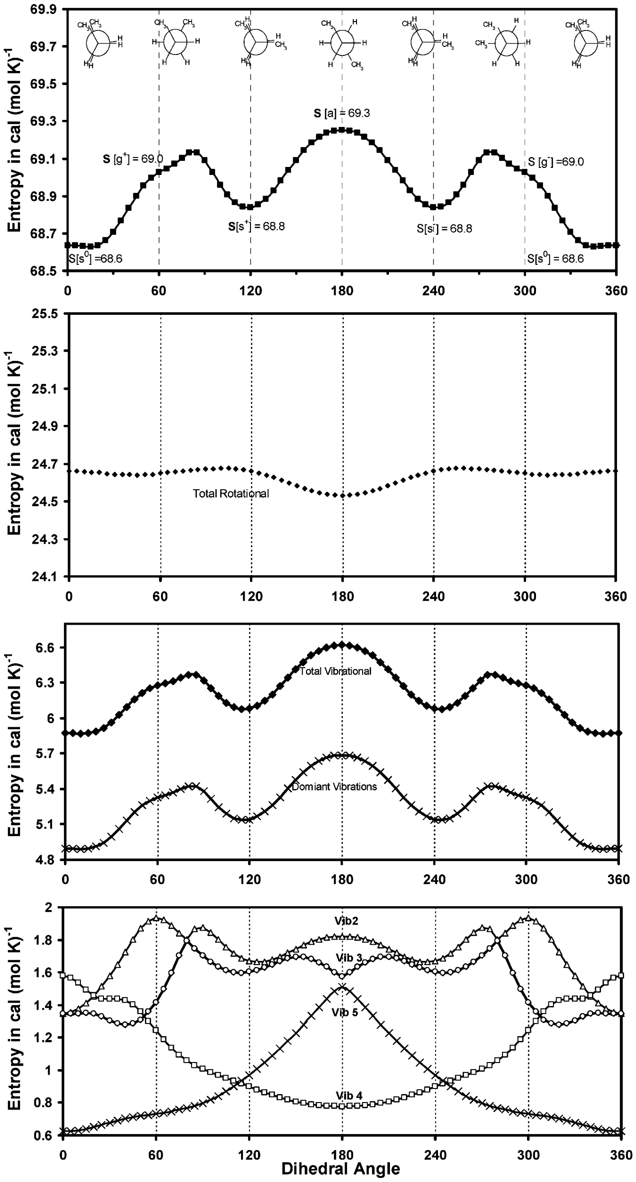

Figure 6. Entropy component computed at the CBS4 level of theory as a function of reaction coordinate (C2−C3 dihedral angle).

The most famous equation of statistical mechanics is the Boltzmann[21] equation:

$$S = R \ln W \tag{6}$$

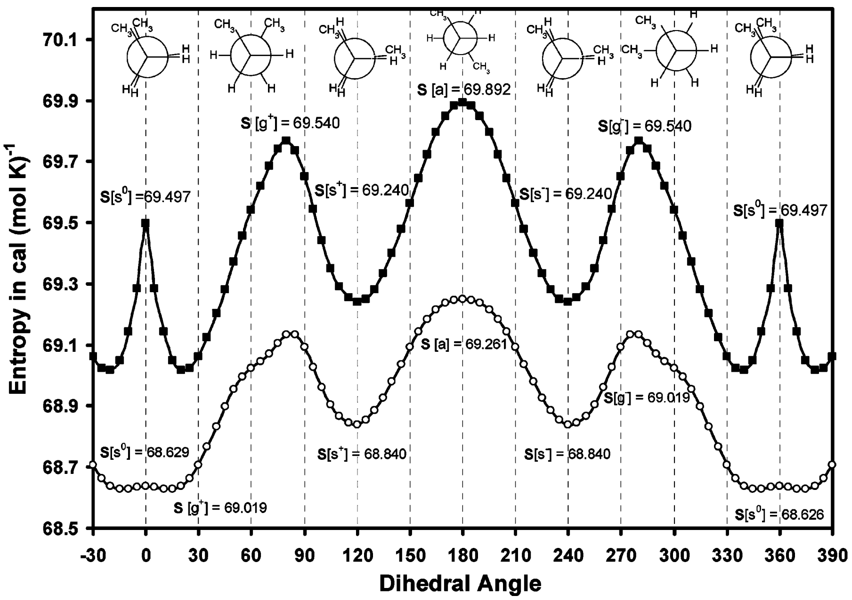

Figure 7. Comparison of entropy curves computed at CBS4 (lower curve) and MP2 (upper curve) levels of theory containing $3N - 7$ internal degrees of freedom without symmetry contribution. Tight geometry optimization was used throughout and in the vicinity of 0° dihedral angle; grid points were computed in 1° intervals.

where R is the universal gas constant (1.98 cal/mol K) for an Avogadro number of molecules and W is the extent of disorder. The inverse of disorder ($1/W$) is to be regarded as the extent of "order". Following the suggestion of Schrödinger,[22] relative information can be related to order, and therefore to entropy, in this relation:

$$(I/I_0) = (1/W) = \exp(-S/R) \tag{7}$$

Note that "I" is the information present in a particular structure and "I_0" is the information present in a reference structure. Similarly, this equivalence can be displayed as an alternative functional dependence in logarithmic form:

$$\ln I = (-1/R)S + \ln I_0 \tag{8}$$

Considering the entropy change associated with a process of going from one arbitrary point (No. 1) to another (No. 2) the entropy change may be written as follows:

$$\Delta S[1 \rightarrow 2] = S[2] - S[1] = R\,[\ln(I_0/I_2) - \ln(I_0/I_1)] = -R\ln(I_2/I_1) \tag{9}$$

On progressing from the anti (180°) to the gauche$^+$ (60°) conformation, we may have the following logarithmic form:

$$\ln I_{60°} = -(1/R)\Delta S + \ln I_{180°} \tag{10}$$

The exponential and logarithmic forms of eq 10 are plotted in Figure 8 for *n*-butane. Various folded molecular structures contain different amounts of information. The relative amount of information may be related to the relative entropy or the entropy change. It appears that the g^+ or g^- conformers contain approximately 16% more information than the anti-structure. Furthermore, the syn conformation with the two groups eclipsed contained about 42% more information than the fully staggered anti orientation. From the results presented in Figure 8, it is inevitable to conclude that during the folding process, that is, on going from the fully extended or anti (180°) form via the gauche (60°) form, toward the fully folded or syn° (0°) form, information increases within the system.

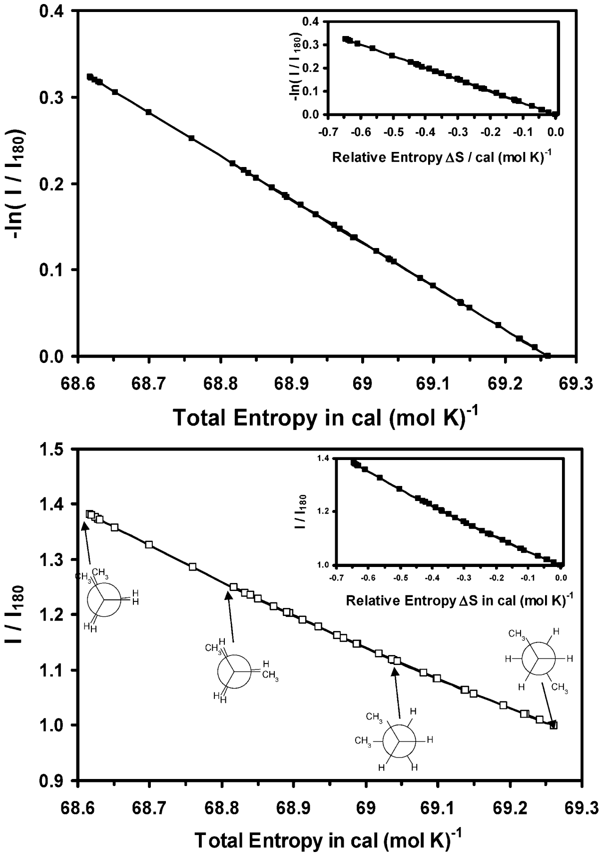

Figure 8. Relative conformational folding information as a function of entropy.

For conversion from the anti conformer to an arbitrary x-conformation we may rewrite eq 10 in the form:

$$\ln\left(\frac{I_{x-\mathrm{conf.}}}{I_{\mathrm{anti}}}\right) = -\left(\frac{\Delta S}{R}\right) \tag{11}$$

Figure 9 shows the amount of information stored in the conformations of *n*-butane as a function of the rotation about

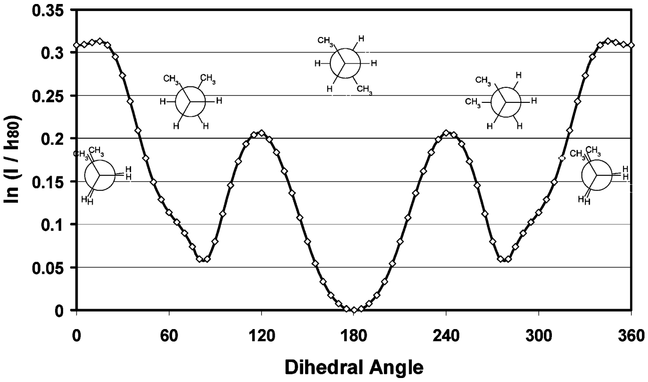

Figure 9. Information content on a logarithmic scale relative to the extended anti conformation as a function of dihedral angle.

the central C−C bond. The difference in natural log of relative information between the gauche $\ln(I_{60}/I_{180}) = 0.07$ and the anti: $\ln(I_{180}/I_{180}) = 0.00$ is simply $-\Delta S/R = 0.07$. This dimensionless number is a measure of the relative quantity of information. It is yet to be determined what portion of $-\Delta S/R$ will be regarded as 1 bit of information.

Consequently, it is clear to assume that information is being fed into a folding system. Such information will manifest itself in different physical characteristics, such as the entropy change of the system, observed after the folding has been accomplished. According to Wheeler, "*all things physical are information theoretic* ... [therefore] ... *information gives rise to physics*".[23]

Conclusion

The conformational entropy calculated from $3N - 7$ internal degrees of freedom was found to be a continuous function of rotational folding. It appeared that each of the two equivalent gauche conformers had 16% more information as the anti conformer. Furthermore the syn conformation with the eclipsed methyl groups contained about 42% more information than the fully staggered anti-orientation. The natural log of the relative information is equivalent to $-(\Delta S/R)$; a dimensionless number in fact measures the quantity, but not the quality, of the information.

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