

Articles

Using a Convenient, Quantitative Model for Torsional Entropy To Establish Qualitative Trends for Molecular Processes That Restrict Conformational Freedom

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A non-quantum-mechanical, readily applied model is described that estimates torsional entropy (S_{tor} , the entropy associated with torsional motions about a single bond) quantitatively. Using this model, torsional entropies are evaluated for a variety of molecular arrangements. Qualitative trends emerge from these estimates that are consistent with chemical intuition. The entropy associated with torsional motion is not constant: values of S_{tor} range from 0 to 15 J mol⁻¹ K⁻¹ and are sensitive to details of the bond around which the torsion occurs. Important characteristics include the bond length, the hybridization, the symmetry, the sizes of these atoms or groups of atoms, and the extent of conjugation to adjacent bonds. These values are relatively independent of one another in a number of important cases, and therefore the total change in conformational entropy for a given process may be estimated by adding changes in entropy due to restricting torsions around individual bonds. A model that permits *quantitative* estimations of changes in conformational entropy will be useful in a wide range of chemical and biochemical applications that include the design of tight-binding polyvalent pharmaceuticals and stable multiparticle molecular assemblies, as well as in the kinetic and thermodynamic analysis of almost any chemical reaction that involves the restriction of the torsions of rotors.

Introduction

We provide an intuitive, readily applied, classical (i.e., non-quantum-mechanical) model for estimating the entropy of torsional motion about a chemical bond. The assumptions of this model are met when the quantized energy of torsional vibration ($h\nu$) is less than kT (empirically, this assumption is met when the energetic barriers separating the torsional minima are less than 40 kJ/mol)¹ and is applicable to most, but not all, single bonds. For torsions with energetic barriers greater than 40 kJ/mol, quantum mechanical effects dominate in most cases, and the torsional motions are approximated well as a quantized vibrations.

Processes in which large numbers of torsional motions become restricted are entropically unfavorable. A large contribution to ΔS in such processes is the change in torsional entropy, ΔS_{tor} . We define the *sum* of changes

in torsional entropies of all the bonds as the *conformational entropy*: $\Delta S_{\text{conf}} \equiv \sum S_{\text{tor}}$. We believe that our model for ΔS_{tor} will be useful in estimating the entropic components to the free energy for molecular processes that involve a change in the degree of restriction of single bonds with low torsional barriers. Examples of such processes (Figure 1) may include binding of flexible substrates to enzymes,² the chelate effect,³ reactions with enhanced rates due to intramolecularity,^{4,5} cyclizations of saturated linear chains,⁶ adsorption of flexible, long-chain alkanes onto metallic surfaces to form a 2-dimensional monolayer,⁷ melting of solids into liquids and subliming of solids into gases,^{8,9} transfer of flexible hydrophobic molecules from water into organic solvent,^{10,11} self-assembly of multiple flexible particles to make a stable aggregate in solution,^{12,13} folding of

(1) The rate of rotation is correlated by transition state theory to the energetic barrier to rotation (the rate of rotation equals $k_{\text{tor}} = \kappa kT / h \exp(\Delta E_{\text{barrier}}/kT)$, where ΔE is the energetic barrier to rotation). The energetic barrier to rotation has been empirically correlated to the entropy of rotation about a single bond (see: Guggenheim, E. A. *Trans. Faraday Soc.* **1940**, 97). These correlations are only approximate because the value of the torsional entropy for a bond estimated from its energetic barrier depends on the model one uses for the shape of the torsional energy wells. The shape of the torsional well has been fit to a number of functions. For example, $U = U_0 \sin^2(\Phi)$, where U is the internal energy, U_0 is the maximum internal energy (J/mol, referenced to $U = 0$ at the torsional global minimum), and Φ is the torsional angle (rad) (Guggenheim). The validity of this shape has been questioned (see: Blade, E., Kimball, G. E. *J. Chem. Phys.* **1950**, 18, 630). In our work, we make *no assumption* about the shape of the well (see Appendix 1). Nevertheless, the wide range in the rates of rotation about a single bond serve as a qualitative illustration that the entropies of torsional motion may not be all the same.

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 (3) For recent discussions, see: Myers, R. T. *Inorg. Chem.* **1978**, 17, 952–970.
 (4) Mandolini, L. *Adv. Phys. Org. Chem.* **1986**, 22, 1–111.
 (5) Page, M. I.; Jencks, W. P. *Gaz. Chim. Ital.* **1987**, 117, 455–460.
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 (10) Gao, J.; Qiao, S.; Whitesides, G. M. *J. Med. Chem.* **1995**, 38, 2292–2301.
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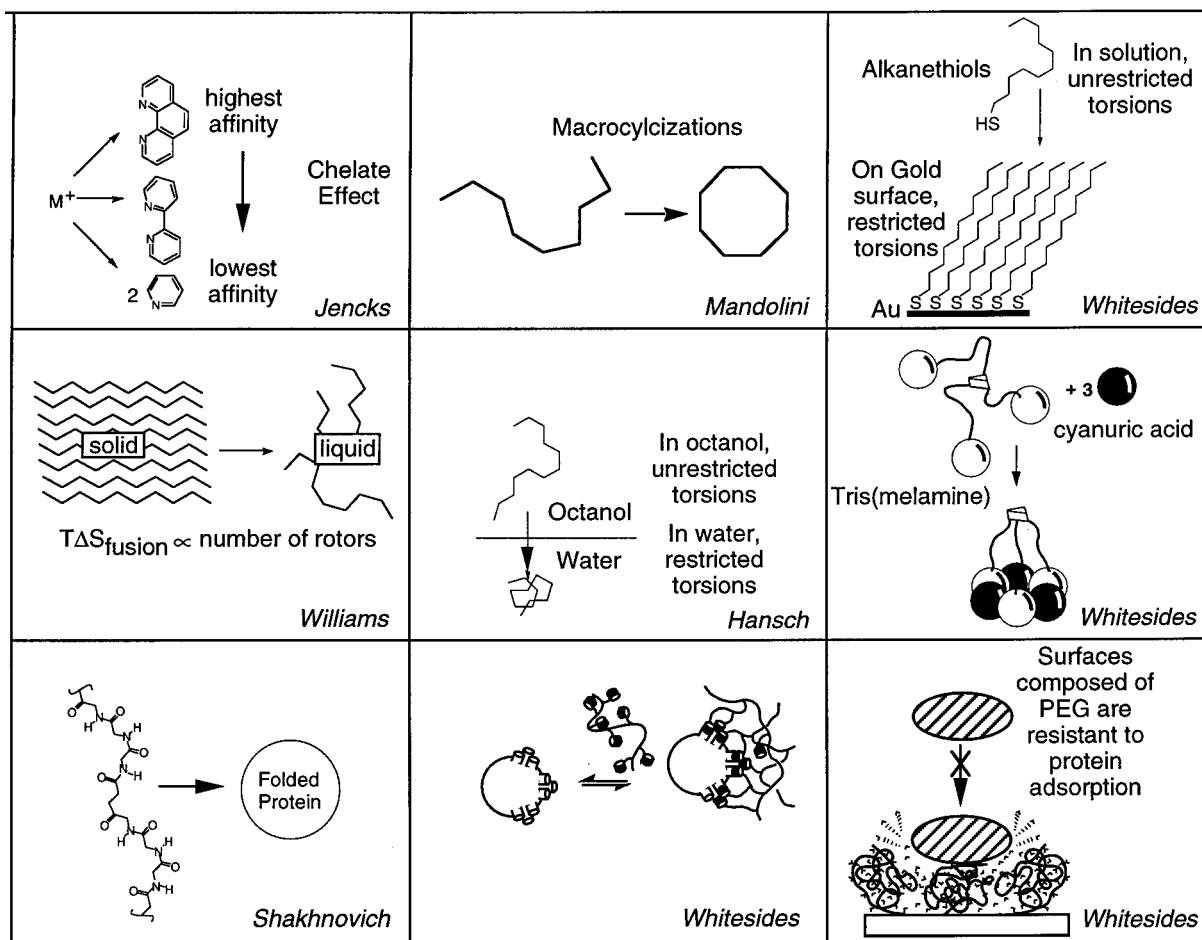


Figure 1. Illustrations of some synthetic and natural processes in which torsions are restricted. See text for references.

proteins,^{14–16} interactions of divalent antibodies with polyvalent surfaces,¹⁷ binding of ligands (especially those that are polyvalent) to receptors,^{18–21} and the interaction of a protein with a polymeric, well-hydrated protein-resistant surface.^{22–24}

Classification of All Single Bonds as “Free” or “Rigid”. Jencks has suggested that the complete restriction (freezing) of torsional motion around a single bond occurs with an entropic cost of $\sim 18 \text{ J mol}^{-1} \text{ K}^{-1}$.²⁵

(14) Karplus, M.; Shakhnovich, E. In *Protein Folding: Theoretical Studies of Thermodynamics and Dynamics*; Creighton, T., Ed.; W.H. Freeman and Company: New York, 1992; pp 127–196.

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(16) Hagler, A. T.; Stern, P. S.; Sharon, R.; Becker, J. M.; Naidler, F. *J. Am. Chem. Soc.* **1979**, *101*, 6842–6852.

(17) Karush, F. *Compr. Immunol.* **1978**, *5*, 85–116.

(18) Miranker, A.; Karplus, M. *Proteins* **1995**, *23*, 472–490.

(19) Desjarlais, R. L.; Sheridan, R. P.; Dixon, J. S.; Kuntz, I. D.; Venkataraghavan, R. *J. Med. Chem.* **1986**, *29*, 2149–2153.

(20) Stack, T. D. P.; Hou, Z.; Raymond, K. N. *J. Am. Chem. Soc.* **1993**, *115*, 6466–6467.

(21) Mammen, M.; Dahmann, G.; Whitesides, G. M. *J. Med. Chem.* **1995**, *38*, 4179–4190.

(22) Mrksich, M.; Whitesides, G. M. *Tr. Biotech.* **1995**, *13*, 228–235.

(23) Mrksich, M.; Sigal, G. B.; Whitesides, G. M. *Langmuir* **1995**, *11*, 4383–4385.

(24) Prime, K. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1993**, *115*, 10714–10721.

(25) Jencks reported a value of 17–19 $\text{J mol}^{-1} \text{ K}^{-1}$. Page, M. I.; Jencks, W. P. *Proc. Nat. Acad. Sci. U.S.A.* **1971**, *68*, 1678. Since this range of values is meant to apply to chemical processes, it corresponds to the expected change in torsional entropy on restriction of a free rotor corresponding the potential energy component of entropy. In his work, as in our work, the kinetic energy component of torsional entropy is ignored because it remains constant for most chemical processes.

An underlying assumption of this assertion is that the value for torsional entropy is constant for all single bonds. In this zeroth level approximation, all single bonds are first classified as either “free” (undergoing unrestricted torsional motion) or “rigid” (not undergoing torsional motion). Higher order bonds (e.g., double bonds, triple bonds, and aromatic bonds) are classified as “rigid”. If this suggestion is correct, it follows that a crude estimate of the value of ΔS_{conf} , assuming additivity of the torsional entropies, is $18 N \text{ J mol}^{-1} \text{ K}^{-1}$, where N is the total number of torsions restricted by the process under investigation.

There have been few studies in which the entropy and enthalpy of a torsional process have been measured carefully. These studies are not consistent with the proposals of Jencks: in general, $18N \text{ J mol}^{-1} \text{ K}^{-1}$ is an *overestimate* of the entropic cost of torsional restriction.^{26–33}

Truhlar and Pitzer suggested that the potential energy component of torsional entropy can be calculated from a flat potential energy surface (a surface for which the energy is the same at every torsional angle) and would equal $R \ln(2\pi) = 15.28 \text{ J mol}^{-1} \text{ K}^{-1}$. This value is approximately the same as that suggested by Jencks and Truhlar: Pitzer, K. S.; Gwinn, W. D. *J. Chem. Phys.* **1942**, *10*, 428. Truhlar, D. G. *J. Comput. Chem.* **1991**, *12*, 266.

(26) Mizushima, S. *Structure of Molecules and Internal Rotation*; Academic Press: New York, 1954.

(27) Starkweather, H. W.; Boyd, R. H. *J. Phys. Chem.* **1960**, *64*, 410–418.

(28) Guggenheim, E. A. *Boltzmann's Distribution Law*; North-Holland Publishing Company: Amsterdam, 1955.

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Quantitation of the Degree of Torsional Freedom.

A single bond is neither strictly a free rotor nor strictly rigid.³⁴ In this paper, we define quantitatively the extent to which a bond is fixed by its torsional entropy; the more freely the bond rotates, the greater its torsional entropy. Noninteracting solvent does not appear to alter vibrations or torsions.^{35,36} It has been suggested that there are empirical relationships between the torsional entropy and both the rate of rotation around a single bond and the energetic barrier to rotation.¹ Some single bonds, such as the carbon–sulfur bond, rotate very rapidly ($\sim 4 \times 10^{12} \text{ s}^{-1}$) because a very small barrier ($\sim 1 \text{ kJ/mol}$) exists between the torsional minima; these bonds, in general, have large torsional entropies. Other single bonds, such as the secondary amide bond, rotate very slowly (1 s^{-1}) due to a high energy barrier ($\sim 75 \text{ kJ/mol}$) between minima; these bonds, in general, have small torsional entropies.^{1,37}

Current computational approaches to estimating total conformational entropy have two limitations: first, torsional—defined as every possible arrangement of torsional positions within a molecule—for molecules that have even a few single bonds is large ($\sim 3^N$ for N single bonds),³⁸ and thus mapping this space computationally is generally prohibitively expensive in computer time; second, the energetic surface for torsional motion is often asymmetric and inconsistent with harmonic motion (torsional motion is often poorly modeled as a harmonic oscillation).³⁴

Conformational entropy is not a component of vibrational entropy.³⁹ We define vibrations as motions that occur in deep energetic minima; these motions are best described *quantum mechanically*⁴⁰ and contribute insignificantly to the changes in entropy for most molecular processes.⁴¹ Torsional motions, however, are often best described *classically*,^{42,43} and contribute significantly to the changes in entropy for these same processes. In fact, Truhlar has suggested that the quantum mechanical treatment of torsions can yield grossly inaccurate values for S_{tor} if the motion is modeled as a vibrating spring with a weak spring constant; this point again suggests that torsions are modeled poorly as vibrations.³⁴

We evaluate torsional entropy independently of any

model imposed on the nature of the motion in any part of the torsional space; that is, we do not assume that the motion is harmonic, oscillatory, or restricted to the lowest energy well.¹ The torsional entropy from our model is a function of the depth, breadth, and number of minima in the torsional landscape. Previous work that has attempted to estimate torsional entropies simply from barriers to rotation have failed, mainly because of the significant influence of the breadth and shape of the well on the value of S_{tor} .^{1,44}

This paper is organized into two sections. First, we derive our model of torsional entropy, and we verify its assumptions; the major assumption is that quantum mechanical effects are negligible in most cases. Second, we apply this model for torsional entropy to torsions of isolated molecules in a number of intramolecular environments and describe the qualitative patterns that emerge; these patterns are consistent with chemical intuition.

Determining the Entropy of Torsional Motion from a Plot of Potential Energy as a Function of Torsional Angle. Our model for torsional entropy is based only on potential energy. We ignore the kinetic energy terms because they are a function only of the mass and the temperature of the system, which are, for most processes, constant. Thus the *changes* in torsional entropy reflect changes in its potential energy component: as chemists, we are generally interested in values of ΔS_{tor} and not in absolute values of S_{tor} .⁴⁵

In this paper, we estimate the value of S_{tor} of a bond from a potential energy map (eq 1, Figure 2) describing rotation about that bond.⁴⁶ The probability P (unitless) that the torsion is at torsional angle Φ (rad) depends on both its energy E (J, relative to the lowest energy state) and the temperature T (K) (eq 1).

$$S_{\text{tor}} = \int_{\Phi=0}^{2\pi} P \ln P \, d\Phi \quad (1)$$

where

$$P = \frac{e^{-E/KT}}{\int_{\Phi=0}^{2\pi} e^{-E/KT} \, d\Phi}$$

We obtain this map of energy as a function of torsional angle Φ by performing a torsional sweep of 2π radians about a single bond in steps of 0.01 radian. At each step,

(30) Temperley, H. N. V. *J. Res. Natl. Bur. Stand.* **1956**, *56*, 55–70.

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(32) Taylor, W. J. *J. Chem. Phys.* **1948**, *16*, 257–265.

(33) The experimental value for the average torsional entropy of the bonds in polyethyleneglycol is $6.4 \text{ J mol}^{-1} \text{ K}^{-1}$. Yoshiharu, T.; Nose, T.; Hata, T. *Polym. J.* **1974**, *6*, 51–55.

(34) Truhlar, D. G. *J. Comput. Chem.* **1991**, *12*, 266–270.

(35) Frank, H. S.; Evans, M. W. *J. Chem. Phys.* **1945**, *13*, 507–532.

(36) Wertz, D. H. *J. Am. Chem. Soc.* **1980**, *102*, 5316–5318.

(37) *Physical Chemistry*; Laidler, K. J., Meiser, J. H., Eds.; Benjamin/Cummings Publishing Co., Inc.: Toronto, 1982.

(38) Edholm, O.; Berendsen, J. C. *Mol. Phys.* **1984**, *51*, 1011–1028.

(39) Steinberg, I. Z.; Scheraga, H. A. *J. Biol. Chem.* **1963**, *238*, 172–181.

(40) These high-frequency motions can *not* occur at all possible energies defined by a potential energy map: they generally occupy only a single state corresponding to a single energy near each of the minima. Low-frequency motions, however, have a density of energy states that is sufficiently high that we can model the motion classically: the motion can occur at any energy defined by a potential energy map.

(41) The Einstein equation describes an exact relationship between the frequency of vibration (ν , cm^{-1}) and the entropy associated with that vibration (S_{vib} , $\text{J mol}^{-1} \text{ K}^{-1}$). The higher the value of ν , the lower the value of S_{vib} . For $S_{\text{vib}} > 100 \text{ cm}^{-1}$, the value of TS_{vib} at room temperature is less than 4 kJ/mol .

(42) Pitzer, K. S. *J. Chem. Phys.* **1946**, *14*, 239–243.

(43) Kemp, J. D.; Pitzer, K. S. *J. Chem. Phys.* **1937**, *69*, 276–279.

(44) The minimization included 50 steps of Adopted-Basis Newton Raphson using the CHARMM forcefield.

(45) The absolute value of S_{tor} is the sum of the components due to potential energy and due to kinetic energy. In certain compilations of experimental thermodynamic values, the total entropies of torsions are tabulated. These values are, for example, approximately $12 \text{ J mol}^{-1} \text{ K}^{-1}$ for each methylene group in the melting of straight alkanes of length N carbons, for values of N over a wide range. A crude estimate of the kinetic energy component at room temperature is $5 \text{ J mol}^{-1} \text{ K}^{-1}$. The experimental value of the torsional entropy due only to potential energy for straight alkanes is then approximately the same as that calculated theoretically in our work $\sim 7 \text{ J mol}^{-1} \text{ K}^{-1}$. A value of $11.97 \text{ J mol}^{-1} \text{ K}^{-1}$ per methylene is reported in Pitzer, K. *J. Chem. Phys.* **1940**, *8*, 711. A value of $12.35 \text{ J mol}^{-1} \text{ K}^{-1}$ is reported in Person, W. B.; Pimentel, G. C. *J. Am. Chem. Soc.* **1952**, *75*, 532.

(46) Such maps are often described as adiabatic potential energy surfaces. These maps assume that the Born–Oppenheimer approximation holds; that is, the electronic states equilibrate much faster than the nuclear ones. The internal energy at each torsional angle in such a map is minimized using CHARMM as described in the text. Accurate adiabatic maps can be obtained with most force fields and with a relatively modest level of theory; Schleyer, P. R.; Kaupp, M.; Hampel, F.; Bremer, M.; Mislow, K. *J. Am. Chem. Soc.* **1992**, *114*, 6791–6797.

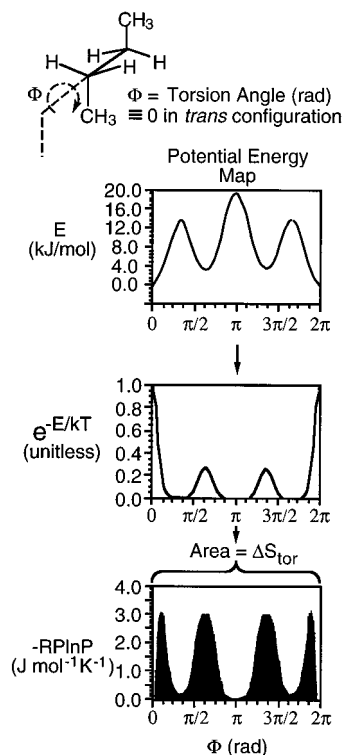


Figure 2. Schematic of the derivation of torsional entropy from a torsional map of energy versus torsional angle Φ . Appendix 1 provides mathematical detail. The value of Φ is defined as zero for the trans configuration of butane.

we minimize the molecular structure using a CHARMM forcefield,⁴⁴ and determine the energy of the minimized structure. This procedure is equivalent to evaluation of the potential of mean force. It may be accurate for relatively small molecules where steric overlap between distant parts of the molecule is not likely to be a crucial factor in restricting conformational space. Appendix 1 derives eq 1 from the statistical mechanical relationships between entropy, free energy, and the partition function for torsional motion. Appendix 2 provides mathematical evidence that the *integral* form of eq 1 is acceptable because the density of states in the torsional wells of interest is sufficiently dense; that is, we can ignore quantum mechanical effects in describing the torsional motions of *most* single bonds. Figure 3 illustrates the close spacing between the quantized levels for the center (C_2-C_3) torsion of butane.

Hopfinger et al. have derived and used a summation (rather than integral) form of a formula structurally similar to eq 1 to estimate the glass transition temperatures of certain polymers.⁴⁷ With long chain polymers comes the difficulty of accounting for intrachain interactions and the introduction of complex additivity rules. Most of the examples in the present work are of small molecules, and the intended applications lie in the field of ligand design (especially oligovalent ligands that bind oligovalent receptors) and not polymer biophysics.

The Torsional Entropies of n -Alkanes Are Independent of Chain Length and Position in the Chain. We perform two sorts of computational experiments that explore the extent to which torsions within a

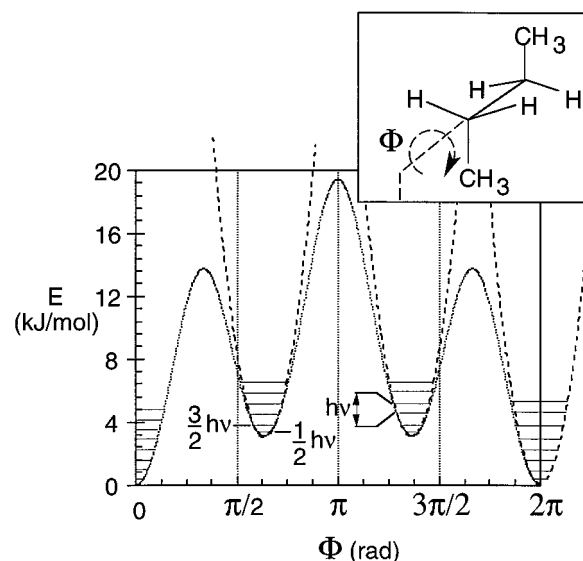


Figure 3. Potential energy map for the center (C_2-C_3) torsion of butane, showing the energy spacing $h\nu$ (kJ/mol) between the quantized levels; $h\nu \sim 0.8$ kJ/mol. The density of states is sufficiently high (multiple vibrational levels are occupied) so that the integral form of eq 1 is valid ($kT = 2.5$ kJ/mol). Appendix 2 provides detail of the derivation of the model used to estimate the energy spacings in energy wells. The value of Φ is defined as zero for trans configuration of butane.

Table 1. Values of S_{tor} ($\text{J mol}^{-1} \text{K}^{-1}$) for the Center Torsion in Straight-Chain Alkanes of Varying Length, $C_n\text{H}_{2n+2}$, and for Every Torsion within Hexadecane, $C_{16}\text{H}_{34}$

middle rotation in $C_n\text{H}_{2n+2}$		$C(x-y)$ in $C_{16}\text{H}_{34}$	
n	S_{tor}	$x-y$	S_{tor}
4	7.3	2-3	7.0
6	6.5	3-4	6.6
8	6.7	4-5	6.7
10	6.8	5-6	6.7
12	6.6	6-7	6.6
16	6.7	7-8	6.6
		8-9	6.7

molecule are independent of one another. First, we estimate the torsional entropy of the center torsion for a series of linear alkanes of varying length. The conclusion from these calculations is that the torsional entropies are approximately constant (Table 1). Second, we estimate the torsional entropy of every torsion in linear hexadecane.³³ The conclusion here is that, with the exception of the terminal C-C bond, the entropies of the different torsions in the chain are approximately constant (Table 1). Certainly, not all torsions will in all circumstances be independent of one another. In any structure with strong interactions between components along the torsional backbone (e.g., hydrogen bonding between amide groups in the alpha helix of α protein), the torsions will depend significantly on one another and will not be additive.⁴⁸

The conformational entropy for such straight chain alkanes (containing N carbons) have been estimated on the basis of the *experimental* entropy of melting (ΔS_{melt})

(47) Hopfinger, A. J.; Koehler, M. G.; Pearlstein, R. A. *J. Polym. Sci. Part B Polym. Phys.* **1988**, *26*, 2007-2028.

(48) In the case where two torsions are suspected of being coupled, eq 1 can be applied to check the assumption of independence. Eq 1 is applied to torsions in two model molecules. The first molecule contains one of the two torsions; the second molecule will contain both torsions. If the values for ΔS_{tor} differ significantly between the two test molecules, then the assumption of additivity is not valid.

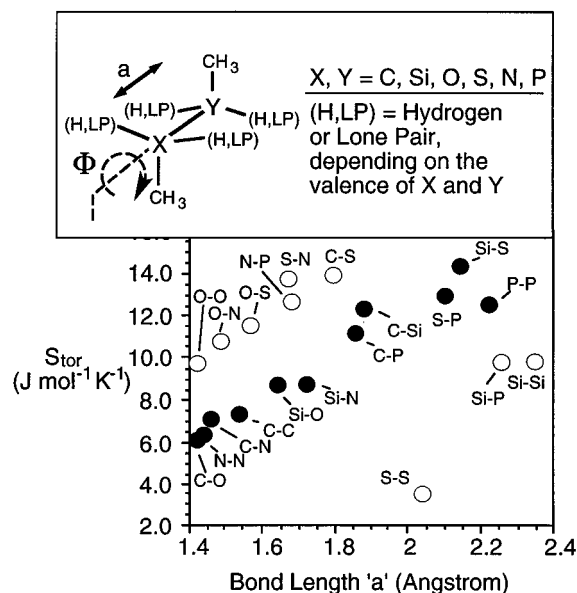


Figure 4. Bond length correlates with torsional entropy. Each point is labeled as X–Y. Three groups of torsions are identified; within all three groups, the value of S_{tor} ($\text{J mol}^{-1} \text{K}^{-1}$) increases with increasing bond length of X–Y. The size of the circles indicates the uncertainties in the values of S_{tor} .

and are in the range $\Delta S_{\text{melt}}/(N - 2) \sim 6.65\text{--}7.11 \text{ J mol}^{-1} \text{K}^{-1}$ per torsion; these values are approximately the same as those calculated using eq 1.^{8,26,27,31,32,45,49} Experimentally, there is only a small dependence of the value of $\Delta S_{\text{melt}}/(N - 2)$ on chain length N : this observation is consistent with our finding in this work that the values of S_{tor} within a straight chain alkane are relatively independent of one another.^{8,26,27,31,32,49,50}

Bond Length Correlates with Torsional Entropy. We estimated the torsional entropy for the series of molecules described by the formula $\text{CH}_3\text{-X-Y-CH}_3$ (where X, Y = C, Si, S, O, N, and P, with each atom being sp^3 hybridized and supporting the appropriate number of hydrogen atoms) (Figure 4). All the molecules appear to fall into one of three groups where within each group, the value of S_{tor} varies linearly with bond length, a (Å). We do not, at this time, propose a rationalization for the spontaneous disaggregation of the data into three groups. The likelihood of hyperconjugation between adjacent orbitals of different size and symmetry may play a role in the barrier heights and therefore in the value of S_{tor} .⁵¹ The general correlation with bond length is intuitively reasonable since the barriers to torsional motion are, in part, determined by steric interactions that occur at eclipsed conformations. Notable is the difference in torsional entropy between C–S and S–S, both single bonds: freezing the C–S bond is four times more costly entropically than freezing the S–S bond.

Schleyer et al. have experimentally measured the energetic barriers to torsional rotation for all 14 congeners of $\text{H}_3\text{X-YH}_3$, where X, Y = C, Si, Ge, Sn, and Pb.⁵¹ Although no reliable method of converting rotational barrier to torsional entropy exists,¹ it is pointed out in this work and others that torsional entropy generally

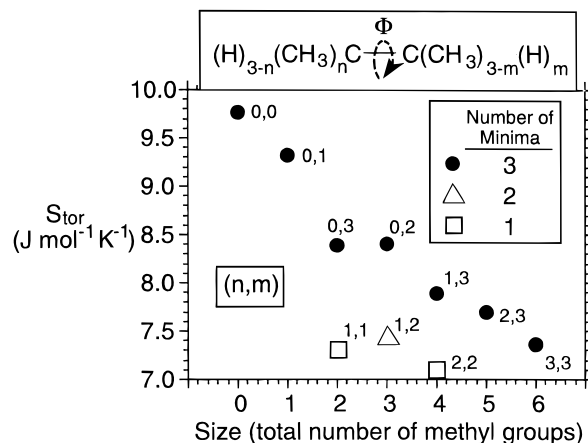


Figure 5. The value of S_{tor} correlates with both the number of substituents and the symmetry of the substitution. The hydrogens of ethane are substituted with methyl groups, and S_{tor} ($\text{J mol}^{-1} \text{K}^{-1}$) of the original C–C bond is estimated using eq 1; the values of S_{tor} correlated with the number of methyl substituents. Molecules that have fewer than three isoenergetic wells have significantly lower values of S_{tor} than expected on the basis of this correlation.

increases with decreasing energetic barrier to torsional motion.¹ If this assertion is correct, the experimental barrier heights reported by Schleyer for the congeners of $\text{H}_3\text{X-YH}_3$ are consistent with the values for torsional entropy estimated for them using eq 1.

Both the Number of Substituents and the Symmetry of Substitution Around a Single Bond Correlates with Torsional Entropy. We explored the sensitivity of torsional entropy to the bulk and the symmetry of substitution around a single C–C bond, using substituted ethane as a model. We determined torsional entropies for molecules described by the $(\text{H})_{3-n}(\text{H}_3\text{C})_n\text{C-C}(\text{CH}_3)_m(\text{H})_{3-m}$; that is, we estimated values of S_{tor} for all molecules from ethane to 2,2,3,3-tetramethylbutane. Figure 5 illustrates the results. The primary conclusion is that the number of methyl groups ($= m + n$; related to the total *bulk* of the substituents) around the center carbon–carbon bond appears to correlate linearly with the torsional entropy of that bond. There are three exceptions to this generalization, and these can be rationalized in terms of their symmetry. The number of substituents determines the torsional entropy for every torsion in this set of examples where there exist three minima of equal energy. Substitution patterns that result in *fewer* than three isoenergetic minima decrease the torsional entropy significantly from that expected on the basis of just the number of substituents: restriction to a single minimum results in more restricted motion and lower torsional entropy than restriction to multiple minima. For example, the value of S_{tor} for fully substituted ethane (2,2,3,3-tetramethylbutane; $m = n = 3$; three global minima) is approximately the same as that of butane ($m = n = 1$; one global minimum), in spite of the much greater bulk of methyl groups over hydrogen atoms.

Both Hybridization of and Electronic Conjugation between the Atoms around Which the Torsion Occurs Correlates Predictably with Torsional Entropy. First, we evaluated the influence of the hybridization of the carbons comprising a torsion (Table 2). We examined torsions of the type $\text{sp}^3\text{-sp}^m$ where m varied from 1 to 3. The value of S_{tor} increased with decreasing

(49) Smith, R. P. *J. Polym. Sci. A* **1966**, 2–4, 869–880.

(50) Dempster, A. B.; Price, K.; Sheppard, N. *J. Magn. Reson.* **1974**, 16, 235–242.

(51) Schleyer, P. R.; Kaupp, M.; Hampel, F.; Bremer, M.; Mislou, K. *J. Am. Chem. Soc.* **1992**, 114, 6791–6797.

Table 2. Values of S_{tor} ($\text{J mol}^{-1} \text{K}^{-1}$) for Torsions Containing Two Carbons with Varying Hybridization (sp to sp³) Were Estimated Using eq 1^a

Hybridization	Molecule	S_{tor}	Comments
sp ² -sp ³		7.3	
sp ³ -sp ²		12.1	
sp ³ -sp ²		12.2	
sp ³ -sp		15.0	
sp ³ -sp ²		15.0	
sp ² -sp ²		6.0	
sp-sp		6.4	
sp ² -sp ²		6.4	
sp ² -sp ²		7.8	
sp ² -sp		9.6	
sp ² -sp ²		10.9	
sp ² -sp ²		11.8	
sp ² -sp ²		0.6	strong dipole-dipole interaction

^a The torsional entropy correlates predictably with state of hybridization. The order of the extent of conjugation (overlap of adjacent orbitals) is that expected based on chemical intuition and is meant to be a qualitative guide to the eye. The torsional entropy appears to decrease with increasing conjugation between adjacent bonds.

values of m . We rationalize this correlation with both steric effects and symmetry: in the order sp³ > sp² > sp, steric repulsion in the eclipsed state goes from highest to lowest; in the same order, symmetry of the bond increases and goes from a 3-fold, to a 6-fold, to a completely cylindrically symmetric torsion. We do not at this time know whether the arguments based on steric effects are more or less important than those based on symmetry.

Second, we illustrate the importance of electronic conjugation (overlap of adjacent p-clouds; magnitude of intervening electron density) by examining a variety of torsions of the type sp^{*n*} - sp^{*m*}, where n and m are either 1 or 2. For the set of molecules where $n = m = 2$ (Table 2), the differences in the value of S_{tor} are due to electronic effects and not to hybridization (hybridization is constant). For this set, the degree of conjugation appears to correlate inversely with the magnitude of S_{tor} . In certain cases, electronic effects other than conjugation may be important: an example is 2-ketopropanal, in which two adjacent carbonyls present two neighboring dipoles that have a strongly preferred orientation; the result is a large barrier to rotation and a low value of S_{tor} . "Electronic Conjugation" can clearly be treated much more rigorously than it has been in this section, but that would not serve the central conclusion here: this set of examples is chosen to illustrate that the physical organic chemist's qualitative concept of bond delocalization helps rationalize and helps to rank order the degree to which single torsions are restricted.

Table 3. Torsional Entropies Are Estimated for Five Classes of Molecules, Illustrating Some of the Patterns That Emerge from This Work

Class of Molecule	Example of Torsion (indicated by curved arrow)	S_{tor} ($\text{J mol}^{-1} \text{K}^{-1}$)
Saturated heteroalkanes		13.9
		7.3
		7.1
		6.1
		3.5
Alkanes (pentane)		7.1
		6.5
Ethers (1,2-dimethoxyethane)		6.1
		8.0
Perfluoroalkanes		0.3
Peptides		6.9
		12.1
		0.8

Conclusions

The widely used rule of thumb that all single bonds are equally flexible and contain equal torsional entropy is wrong and misleading. As an illustration, values of S_{tor} for some common bond types are given in Table 3 (alkanes, ethers, amines, sulfides, peptide bonds, alkyl-aryl bonds, α -carbonyl bonds, etc.). One example is the difference in the values of S_{tor} between a C-S and a S-S bond, both single bonds: freezing the C-S bond is four times more costly entropically than freezing the S-S bond. Such knowledge may be incorporated into the design of molecules prior to multistep synthesis. Perfluorinated alkanes deserve special mention: the van der Waals surfaces of fluoro atoms on adjacent carbons along an n -perfluoroalkane are in contact and interact favorably.⁵² Torsional barriers are very high (>40 kJ/mol) relative to perproteoalkanes (15 kJ/mol), and the single bonds of the perfluoroalkane are "stiff" with $\Delta S_{\text{tor}} < 0.5 \text{ J mol}^{-1} \text{ K}^{-1}$.⁵²⁻⁵⁴

We have provided a simple, intuitive model for torsional entropy that accounts for the detailed potential

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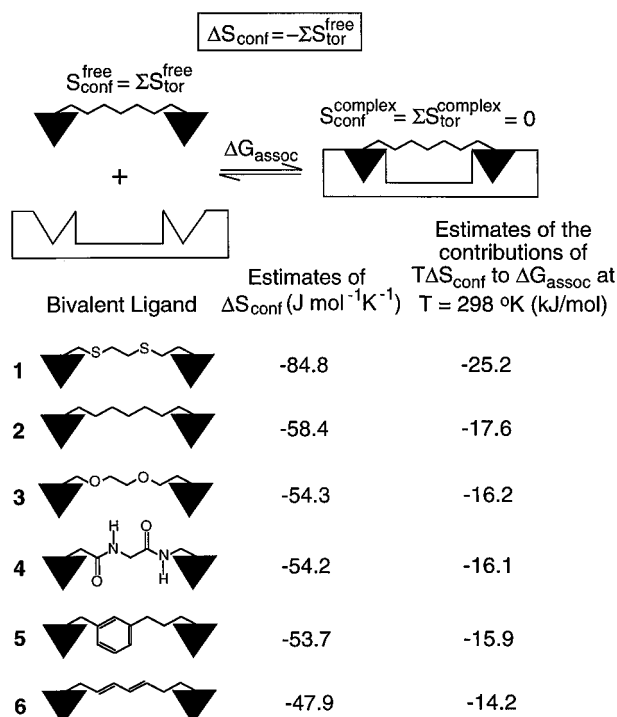


Figure 6. The values of the sum of the $S_{\text{tor}}^{\text{free}}$ ($\Sigma S_{\text{tor}}^{\text{free}}$) are calculated using eq 1 for each of four bivalent ligands prior to complexation. After complexation, the torsions are assumed to be completely restricted so that $\Sigma S_{\text{tor}}^{\text{complex}} = 0$. The total change in conformational entropy, ΔS_{conf} is then estimated as $S_{\text{tor}}^{\text{free}}$.

energy space of a torsion, including the breadth, height, and shape of the energy wells.¹ This entropy is determined by applying eq 1 to a map of energy as a function of torsional angle: this map, in turn, is easily obtained with many well-parameterized molecular mechanics packages.⁴⁶

Certain qualitative patterns emerge that describe the torsional entropy as a function of molecular environment. These patterns may be useful to those interested in the design of complex molecules that lose conformational freedom on binding their target. We believe that our model will help in designing molecules that bind more tightly to their targets by minimizing conformational entropic costs. For example, one may use the patterns that emerge from this work to improve the design of molecules comprised of multiple ligands that are meant to bind tightly to a cellular surface containing multiple receptors.

To illustrate this idea, we describe a hypothetical example in which a bivalent ligand is designed to complex a rigid bivalent target. There are synthetic choices in designing a linker that connects the two ligands, and estimates of the total change in torsional entropy on complexation based on molecular details may help to guide these choices. In this example, it is assumed that this bivalent ligand loses all conformational freedom on binding a rigid bivalent receptor. Figure 6 gives the structures (1–6) and the calculated changes in torsional entropy on complexation of the bivalent ligand with the rigid bivalent receptor for six different linking schemes. Each linker spans approximately 10 Å. The calculated total change in torsional entropy is greatest for **1**, which contains four C–S linkages, due mainly to the relatively

large value of S_{tor} for C–S bonds compared with C–C bonds. The all-carbon octamethylene linker of **2** gives the next greatest value of S_{tor} . The linker containing the ethyleneglycol (EG) group in molecule **3** gives a lower value of S_{tor} than **2**, mainly due to the relatively small value for the C–O bonds compared with C–C bonds. Molecules **4**, **5**, and **6** show three different schemes where the linker is made more rigid than **1**, **2**, and **3** by restricting two bonds. It is unclear initially which strategy will be the more effective one, experimentally or theoretically. We calculate the change in torsional entropy for **4** and **5** to be approximately equal and lower than that of **2**. In both **4** and **5**, two $\text{sp}^3\text{--sp}^3$ bonds are eliminated and two $\text{sp}^3\text{--sp}^2$ bonds are introduced, each of which has a relatively large value of S_{tor} . In comparison with **4** and **5**, molecule **6** also eliminates three $\text{sp}^3\text{--sp}^3$ bonds, but introduces one $\text{sp}^2\text{--sp}^2$ bond and two $\text{sp}^2\text{--sp}^3$ bonds. We suggest that the tradeoffs in **6** are more attractive than those in **4**. Such considerations are not obvious without considering in detail how molecular detail can influence torsional entropy of single bonds. This paper provides the method and some of the detail that makes such considerations possible.

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Appendix 1. Derivation of Equation 1

We derive eq 1 beginning with the statistical mechanical relationships between entropy, free energy, and the partition function for torsional motion (eq 2). The statistical mechanical definition of internal energy, U , is given by eq 3. Combining eqs 2 and 3 yields eq 4. S_{tor} ($\text{J mol}^{-1} \text{K}^{-1}$) is the torsional entropy, q_{tor} (unitless) is the partition function for torsional motion, and $\langle U \rangle$ (J/mol) is the average value of the internal energy—referenced to zero at the torsional global minimum—over all torsional angles Φ (rad). The internal energy (U) is the sum of the potential energy (V) and the kinetic energy. The kinetic energy is constant in all the processes that we consider in this paper (the temperature is constant, and the masses of all species are unchanged). The potential energy component of the total torsional entropy ($S_{\text{tor}}(V)$) is the only *relevant* component. We use eq 5, analogous to eq 4, to describe the potential energy component of the torsional entropy.

$$G_{\text{tor}} = -RT \ln(q_{\text{tor}}) \rightarrow S_{\text{tor}} = -\frac{\partial G_{\text{tor}}}{\partial T} = R \ln(q_{\text{tor}}) + RT \frac{\partial(\ln q_{\text{tor}})}{\partial T} \quad (2)$$

$$\langle U_{\text{tor}} \rangle = RT^2 \frac{\partial(\ln q_{\text{tor}})}{\partial T} \quad (3)$$

$$S_{\text{tor}} = R \ln q_{\text{tor}} + \frac{\langle U_{\text{tor}} \rangle}{T} \quad (4)$$

$$S_{\text{tor}}(V) = R \ln q_{\text{tor}} + \frac{\langle V_{\text{tor}} \rangle}{T} \quad (5)$$

We define the probability density by eq 6. The partition function, q , is then given by eq 7, and eqs 8–9 follow

from combining eqs 3, 5, 6 and 7. The average value of the potential energy is given by eq 10. If we multiply eq 8 by $P(\Phi)$ and integrate over all of torsional space (0– 2π), we arrive at eq 1.

$$P(\Phi) \equiv \frac{e^{-V(\Phi)/RT}}{\int_0^{2\pi} e^{-V(\Phi)/RT} d\Phi} = \frac{e^{-V(\Phi)/RT}}{q} \quad (6)$$

$$q = \frac{e^{-V(\Phi)/RT}}{P(\Phi)} \quad (7)$$

$$\ln q = -\frac{V(\Phi)}{RT} - \ln P(\Phi) \quad (8)$$

$$R \ln q + \frac{V(\Phi)}{T} = -\ln P(\Phi) \quad (9)$$

$$\langle V \rangle = \frac{\int_0^{2\pi} V(\Phi) e^{-V(\Phi)/RT} d\Phi}{\int_0^{2\pi} e^{-V(\Phi)/RT} d\Phi} = \frac{\int_0^{2\pi} V(\Phi) e^{-V(\Phi)/RT} d\Phi}{q} \quad (10)$$

$$-R \int_0^{2\pi} P(\Phi) \ln P(\Phi) d\Phi = R \int_0^{2\pi} P(\Phi) \ln q d\Phi + \frac{\langle V \rangle}{T} = R \ln q + \langle V \rangle / T = S_{\text{tor}} \quad (1)$$

Appendix 2. Determining the Density of States of Torsional Motion

Steep torsional energetic wells correspond to high-frequency vibrations. For such vibrations, the density of states in torsional space is low, and quantum mechanical effects become important. If quantum mechanical effects are important, the integral given by eq 1 is not valid, and a summation of all discrete, quantized states is appropriate.⁵⁵ We show in this section that if the density of states is sufficiently high for most torsions around single bonds, the integral form of eq 1 is valid.^{56,57}

In order to estimate the density of states for a given well, we assume that the well is parabolically shaped (corresponding to a harmonic oscillation) and fit the curves obtained from adiabatic torsional maps to a parabola (eq 11); E is the energy (J/mol), Φ_r is the

torsional angle (rad), and M_0 , M_1 , and M_2 are the adjustable parameters of the fit. From molecular masses of the atomic components undergoing torsional motion, we obtain the reduced moment of inertia, F (eq 12). We obtain values for the frequency of vibration (ν , s^{-1} , eq 13; the units for ν can be converted from s^{-1} to cm^{-1} using $E = hc\nu$), the spring constant (k , kg/s^2 , eq 14), and the energy spacing between the quantized levels ($h\nu$, J/mol, eq 15) from the values determined in eqs 11–14. Figure 3 provides an example of the results and illustrates the spacing between the quantized levels for the C2–C3 torsion of butane.

$$E = M_0 + M_1(\Phi_r) + M_2(\Phi_r)^2 \quad (11)$$

$$\mu = \frac{\sum M_i r_i^2}{\sum r_i^2} \quad (12)$$

$$\nu = \frac{1}{2\pi} \sqrt{\frac{k}{\mu}} \quad (13)$$

$$k = 2M_2 \quad (14)$$

$$h\nu = \text{energy spacing} = 0.30 \sqrt{\frac{M_2}{\mu}} \quad (15)$$

Comparing the spacing of these energy levels to the spacing of energy levels for whole-molecule rotation, we find for *n*-butane that $h\nu$ is approximately 0.75 kJ/mol (63 cm^{-1}) for the gauche well and approximately 0.80 kJ/mol (68 cm^{-1}) for the trans well. Molecular rotation is well approximated by assuming classical (not quantum mechanical) motion. The energy spacing for molecular rotation, $2(J+1)h^2/8p^2I$, is usually only a little lower (3 kJ/mol for H_2 and $< .50$ kJ/mol for small molecules) than that for torsional motion. We conclude that integration (eq 1) is justifiable for most single bonds.⁵⁸ By exploring torsional entropies for a wide range of bonds belonging to a number of classes, we find empirically that quantum mechanical effects are unimportant if the barriers separating the torsional minima are greater than approximately 40 kJ/mol. In any case where it is suspected that quantum mechanical effects may be important, the methods used in this appendix can be employed as a check.

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