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

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In a recent paper in this journal,[1] Whitesides, Mammen, and Shakhnovich (WMS) proposed a non-quantum-mechanical model to obtain a quantitative estimate of the loss of entropy upon restriction of torsional motion about a single bond. I wish to point out, however, that this model, being based on inadequately defined and somewhat arbitrary assumptions, leads to inconsistent results.

To discuss the WMS method in the right perspective, it is useful to briefly recall the fundamentals of internal rotations which were principally established by Pitzer and co-workers.[2–4] Internal rotation problems can be divided into three categories depending on the magnitude of the torsional potential with respect to RT.[5] If the barrier height is very small as compared with RT, then it may be ignored, and the torsional motion corresponds to a free rotation, whose partition function is given by eq 1, where n is the symmetry number for internal rotation, and I_r is the reduced moment of inertia about the rotational axis.

$$Q_f = \frac{1}{n}\left(\frac{8\pi^3 I_r kT}{h^2}\right)^{1/2} \qquad (1)$$

Since entropy is related to the internal partition function by eq 2, the entropic contribution of a free rotor is given by eq 3.

$$S = R \ln Q + RT \frac{\mathrm{d}\ln Q}{\mathrm{d}T} \qquad (2)$$

$$S(Q_f) = R(0.5 + \ln Q_f) \qquad (3)$$

If the potential is very large in comparison with RT, then the torsional motion corresponds to a torsional vibration which may be treated by the harmonic approximation. The quantum mechanical partition function for a harmonic oscillator is given by eq 4 (omitting zero point energy), and the corresponding entropic contribution by the Einstein equation (eq 5). In both equations $x = hc\tilde{\nu}/kT$, where c is the speed of light in cm s^{-1}, and $\tilde{\nu}$ is
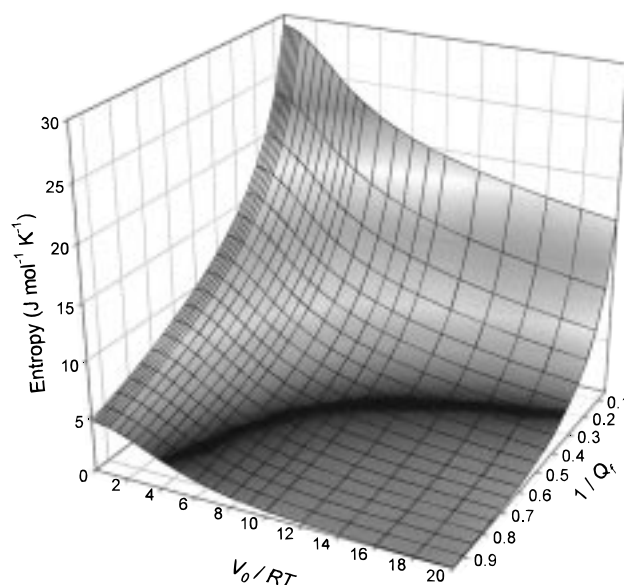
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(1) Mammen, M.; Shakhnovich, E. I.; Whitesides, G. M. *J. Org. Chem.* **1998,** *63,* 3168–3175.
(2) Pitzer, K. S.; Gwinn *J. Chem. Phys* **1942,** *10,* 428–440.
(3) Pitzer, K. S. *J. Chem. Phys* **1946,** *14,* 239–243.
(4) Kilpatrick, J. E.; Pitzer K. S. *J. Chem. Phys* **1949,** *17,* 1064–1075.
(5) (a) Lewis, G. N.; Randall, M.; Pitzer, K. S.; Brewer, L. *Thermodynamics,* 2nd ed.; McGraw-Hill: New York, 1961; Chapter 27. (b) McClelland, B. J. *Statistical Thermodynamics*; Chapman and Hall: London, 1973.

Figure 1. Three-dimensional plot of entropy for a quantum mechanical hindered rotor as a function of V_0/RT [0, 20] and $1/Q_f$ [0.05, 0.95]. Entropy data, calculated by Pitzer and co-workers, are from ref 5a.

the torsional harmonic frequency in cm^{-1}.

$$Q_{\text{HO Quant}} = \frac{1}{1 - e^{-x}} \qquad (4)$$

$$S(Q_{\text{HO Quant}}) = R\left[\frac{x}{e^x - 1} - \ln(1 - e^{-x})\right] \qquad (5)$$

If the potential barrier is neither very large nor very small as compared with RT, then the motion corresponds to a hindered, or restricted, internal rotation. In this case the theory rests upon the numerical solution of the Mathieu equation which results from the one-dimensional Schrödinger equation for a rotor having the torsional potential described by eq 6, where V_0 is the height of the barrier, n is the number of equivalent minima, and ϕ is the torsion angle, chosen so that $\phi = 0$ corresponds to a minimum.[6]

$$V = \frac{V_0}{2}(1 - \cos n\phi) \qquad (6)$$

There are no simple analytic solutions to the hindered rotation problem, but thermodynamic properties, among which entropy, have been presented by Pitzer and co-workers in general tables as a function of two variables, namely the ratio V_0/RT and the reciprocal of free rotor partition function, $1/Q_f$.[2,5,7] A three-dimensional plot of the Pitzer and Gwinn entropy tables is reported in Figure 1. The tables are accurate for molecules with one or more independent internal rotations whose potentials are described by eq 6, i.e., molecules which can be regarded as a rigid frame with attached noninteracting symmetrical tops.[2] To a lower degree of approximation, the

(6) Nielsen, H. H. *Phys. Rev.* **1932,** *40,* 445–456.
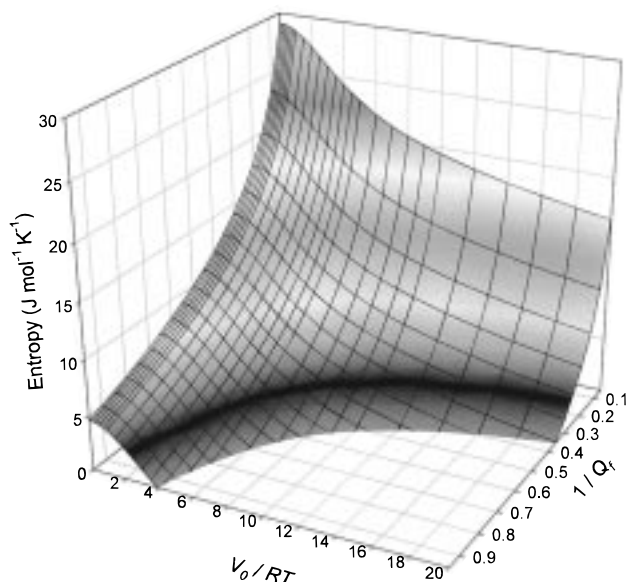(7) Li, J. C. M.; Pitzer, K. S. *J. Phys. Chem.* **1956,** *60,* 466–474.

Figure 2. Three-dimensional plot of entropy for a classical hindered rotor as a function of V_0/RT [0, 20] and $1/Q_f$ [0.05, 0.95]. Negative entropies have not been reported. See text for further details.

tables can also be used in the case of unsymmetrical top internal rotations provided that the potential energies are still described by eq 6.[3] Recently, approximate formulas have been suggested for the partition function of a hindered internal rotation.[8-10]

More complex cases (e.g., rotating groups attached to rotating groups, with no limit upon the symmetry of the groups or upon the number of groups involved in such a sequence; potentials more complex than that shown in eq 6; coupled potentials due to interactions between rotating groups) have been treated by Pitzer and co-workers by an approximation to the quantum mechanical partition function shown in eq 7, where the classical partition function for hindered rotations ($Q_{\text{Hind Class}}$) is scaled by the ratio of the quantum mechanical partition function for harmonic oscillations ($Q_{\text{HO Quant}}$) to its classical counterpart, $Q_{\text{HO Class}}$ ($= x^{-1}$, for a single vibration).[2,4]

$$Q_{\text{Hind Quant}} \approx Q_{\text{Hind Class}}\,[Q_{\text{HO Quant}}/Q_{\text{HO Class}}] \quad (7)$$

For a single rotor, $Q_{\text{Hind Class}}$ is given by an integral over phase space, which, neglecting possible variation of I_r with the twist angle, and integrating over angular momentum, reduces to eq 8.[2,9,10]

$$Q_{\text{Hind Class}} = \frac{Q_f}{2\pi} \int_0^{2\pi} \exp(-V/RT)\mathrm{d}\phi \quad (8)$$

Note that if $V \approx 0$, the integral in eq 8 is equal to 2π, yielding the partition function for a free rotor.

The model proposed by WMS assumes classical behavior (without scaling) and independence of the rotor under examination from other torsions, in other words they assumed, although not explicitly, that the partition function for rotation is adequately expressed by eq 8. In Figure 2 is reported a three-dimensional plot of entropy

for a classical rotor having a hindering potential described by eq 6. The plot has been calculated by numerical solution of eq 2 with the partition function given by eq 8.[11] Comparison of the plot in Figure 2 with that reported in Figure 1 shows that the classical rotor behaves as the quantum mechanical one only for $V_0 = 0$ (free rotation), whereas for $V_0 > 0$ the quantum behavior is approached only in the limit of $1/Q_f$ tending to zero, namely in the cases involving high reduced moment of inertia and/or high temperature. Apart from the case of free rotation, the "classical" entropy is always lower than the "quantum" one, the deviation being more and more important the higher V_0/RT and/or $1/Q_f$. Note that for any finite values of $1/Q_f$, increase of V_0/RT does not lead to zero entropy, but to negative entropy values, which are obviously unrealistic. As an empirical rule, obtained by comparison of the two plots, one can achieve ~ 1 J mol^{-1} K^{-1} accuracy or better on entropy by the classical model if the condition in eq 9 is satisfied.

$$\left(\frac{1}{Q_f} - 0.14\right)\frac{V_0}{RT} < 1.4 \quad (9)$$

Equation 9 thus sets the limits of applicability of the classical model in the range of V_0/RT and $1/Q_f$ values reported in Figure 2.

Following the argument of WMS, let us indicate the integral in eq 8 as the potential energy component of the partition function, Q_V, and the term $Q_f/2\pi$ ($= Q_T$) as the kinetic energy component of the partition function, so that eq 8 can be rewritten as $Q_{\text{Hind Class}} = Q_T Q_V$. According to WMS, freezing of torsional motion does not affect Q_T because this term is a function only of the mass and the temperature of the system; therefore, they assumed that the entropy loss involved in freezing of a rotation (S_{tor}) only depends on the potential energy component of the partition function. In other words they assumed that eq 10 holds.

$$S_{\text{tor}} = S(Q_V) \quad (10)$$

This has been translated into eq 11, where P is the probability [$= \exp(-V/RT)/Q_V$] that the torsion is at torsional angle ϕ.[1]

$$S_{\text{tor}} = -R\int_0^{2\pi} P \ln P \mathrm{d}\phi \quad (11)$$

In practice the method of WMS involves the evaluation of eq 11 on the basis of adiabatic potential energy maps obtained by the CHARMm force field.

It should be clear that restriction of an internal rotation is a thermodynamic process involving an increase of torsional barrier as depicted in Figure 3, in which is illustrated a progressive restriction of torsional motion from free rotation to torsional vibration. Accordingly the entropy loss upon restriction is given by the difference between the initial and the final entropy of internal rotation. The method of WMS, based on eq 10, assumes that both the initial and the final state are adequately described by the classical model, and that the initial entropy is given by $S_i = S(Q_T Q_V) = S(Q_T) + S(Q_V)$,

(8) Truhlar, D. G. *J. Comput. Chem.* **1991**, *12*, 266−270.
(9) McClurg, R. B.; Flagan, R. C.; Goddard, W. A., III. *J. Chem. Phys.* **1997**, *106*, 6675−6680.
(10) Ayala, P. Y.; Schlegel, H. B. *J. Chem. Phys.* **1998**, *108*, 2314−2325.

(11) The entropy values were calculated by an appositely written BASIC program based on Simpson's rule (with 10^3 subintervals) for the numerical evaluation of integrals, and on a finite difference method ($\Delta T = 0.0001$ K) for the numerical evaluation of derivatives.
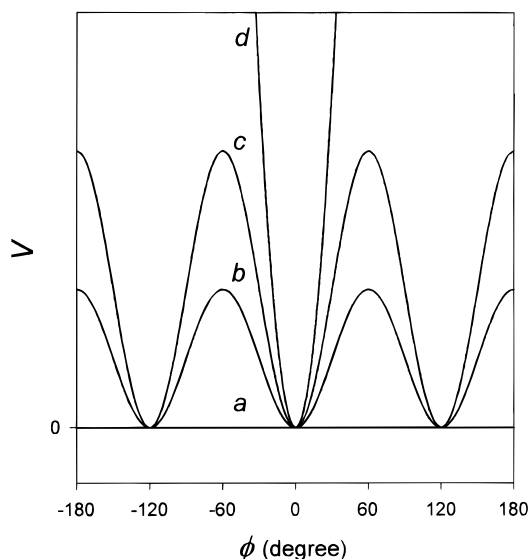
Figure 3. Potential energy curves for an increasingly restricted internal rotation about a generic single bond. Curve *a*: free rotation; curves *b*, *c*: hindered internal rotations; curve *d*: torsional vibration.

whereas the final entropy is given only by $S_f = S(Q_T)$, being the final $S(Q_V) = 0$. I shall return to the meaning of the latter equation later on; for the moment I want only to stress the fact that the model of WMS implies that only a fraction of the entropy that is present in the rotation initially can be lost upon freezing, i.e., that due to the potential energy component of the partition function.

I wish to point out, however, that in the case of complete restriction of torsional motion (freezing) this conclusion is erroneous, because freezing a rotation consists in transforming it into a high frequency torsional vibration as shown in Figure 3. If the initial partition function of a hindered rotor is adequately described by Q_{Hind} (either quantum or classical, depending on the adopted level of sophistication), after restriction, it must be described[12] by $Q_{HO\ Quant}$ so that the involved entropy loss would be given by eq 12.

$$S_{tor} = S(Q_{Hind}) - S(Q_{HO\ Quant}) \qquad (12)$$

Complete restriction, or freezing, of a rotor implies that its motion is transformed into a torsional vibration with a frequency higher than about 1000 cm^{-1}, which has a negligible entropic content at 298.15 K (<0.4 J mol^{-1} K^{-1}, from eq 5). Under this condition eq 12 reduces to eq 13.

$$S_{tor} = S(Q_{Hind}) \qquad (13)$$

Thus the evaluation of the entropy loss involved in freezing of a rotor must be based on the complete partition function (eq 13) and not on its potential energy component only (eq 10) as suggested by WMS. Stated in other words, all the entropy that is present in the rotation initially is lost upon freezing.

Various inconsistencies emerge from the WMS method if it is adopted to evaluate the entropy of freezing of a rotor. For example, eq 11 predicts that freezing of a free rotor ($V \approx 0$, and therefore $P = 1/2\pi$) would involve a constant entropy loss, $S_{tor} = R \ln(2\pi) = 15.28$ J mol^{-1} K^{-1},[13] independently not only from the moments of inertia and symmetries of the rotating groups but also from temperature. This is contrary to the intuitive idea that an increase of temperature increases the average rate of free rotation and therefore the entropy associated to it. Since such entropy will be completely lost upon freezing, S_{tor} cannot be independent from temperature. In fact, S_{tor} for the freezing of a free rotor is given by eq 3, which shows the effects of the temperature, the symmetry, and the reduced moment of inertia. The effect of the latter on entropy is less intuitive than that of temperature. It is well-known that a set of closely spaced energy levels has a higher entropy than a more widely spaced set.[14] An increase of the reduced moment of inertia has the effect of decreasing the spacing between the energy levels of the internal rotation,[5] and thus of increasing its entropy at temperatures above absolute zero. The model proposed by WMS, depending only on the potential energy curve of internal rotation, is independent from the moment of inertia of the rotating groups. Thus, for example, ethane and perdeuteroethane have practically the same potential barrier[15] but different reduced moments of inertia ($I_r = 1.64$ and 3.27 amu Å^2, respectively).[15] The WMS method would predict the same S_{tor} for the two molecules. Using the tables of Pitzer and Gwinn[2] with $V_0 = 12.4$ kJ mol^{-1},[16] and the above I_r values, the obtained torsional entropies ($S_{tor} = 7.0$, and 9.6 J mol^{-1} K^{-1} for C_2H_6, and C_2D_6, respectively) differ by as much as 37%. By the way, the WMS method predicts for ethane a value of S_{tor} of 9.7_5 J mol^{-1} K^{-1} (from Figure 5 of ref 1) which is significantly greater than its *total* torsional entropy (7.0 J mol^{-1} K^{-1}); this point will be discussed later on.

The deficiency of the WMS method in accounting for different reduced moments of inertia is also evident from a comparison of the values of S_{tor} it predicts for ethane and butane (9.7_5 and 7.3 J mol^{-1}K^{-1}, respectively).[1] Since the rotation about the C2–C3 bond in butane has a higher energy barrier than that in ethane, according to the WMS method S_{tor} (C_2H_6) > S_{tor} (C_4H_{10}), once again ignoring the effect of the moments of inertia of the rotating groups. In a careful study on the thermodynamic properties of linear alkanes,[17] in which earlier calculations of Pitzer were revised,[18] Person and Pimentel reported an entropy value at 298.15 K of 18.72 J mol^{-1} K^{-1} for the internal rotation of butane, and 18.92 J mol^{-1} K^{-1} for an internal rotation in an aliphatic chain from

(12) Description of a hindered rotation as a torsional vibration involves an error of ~1 J mol^{-1} K^{-1} or less on entropy if V_0/RT > 6. The error reduces to ~0.5 J mol^{-1} K^{-1} or less if V_0/RT > 10. This results from a comparison of the data plotted in Figure 1 with those obtained by approximating the cosine function in eq 6 to a parabola. From this approximation one obtains $x = (\pi V_0/RT)^{1/2}/Q_f$; that introduced in eq 5 allows the evaluation of $S(Q_{HO\ Quant})$.

(13) In note 25 of ref 1, it would seem that this argument is supported by a suggestion of Pitzer (ref 2) and Truhlar (ref 8), but none of them referred to a potential energy component of torsional entropy.

(14) Maskill, H. *The Physical Basis of Organic Chemistry*; Oxford University: Oxford, 1985; pp 96–98.

(15) Calculated by the MM+ force field, an extension of the MM2 force field, as implemented in version 4.0 of the molecular modeling package HyperChem (Hypercube Inc., Waterloo, Ontario). For an evaluation of the MM+ force field, see: (a) Hocquet, A.; Langgård, M. *J. Mol. Model.* **1998**, *4*, 94–112. For the MM2 force field, see: (b) Allinger, N. *J. Am. Chem. Soc.* **1977**, *99*, 8127–8134.

(16) Chao, R.; Wilhoit, R. C.; Zwolinski, B. J. *J. Phys. Chem. Ref. Data* **1973**, *2*, 427–438.

(17) Person, W. B.; Pimentel, G. C. *J. Am. Chem. Soc.* **1953**, *75*, 532–538.

(18) Pitzer, K. S. *J. Chem. Phys.* **1940**, *8*, 711–720.

heptane to eicosane.[19] The loss of entropy upon freezing an internal rotation in an aliphatic chain is usually the largest contribution to changes in entropy upon cyclization. By examining the entropy changes accompanying ring closure of short alkane chains, O'Neal and Benson estimated that the entropy loss per internal rotation is about 20 J mol^{-1} K^{-1}.[20] Similarly, Jencks and Page estimated a value ranging from 15.5 to 20.5 J mol^{-1} K^{-1}.[21,22] By a large number of experimental entropy data in solution related to several cyclization reaction series involving up to seven rotors, an average value of 16.7 J mol^{-1} K^{-1} per rotor was obtained by Mandolini.[23] All these evaluations are in substantial agreement, and all suggest that the entropic cost of freezing the internal rotation of butane evaluated by WMS is *greatly* underestimated.

WMS claim that the qualitative trends of S_{tor} they obtained are consistent with chemical intuition. In fact, the collective intuition of chemists is strong about energy, but rather weak about entropy. Since the evaluation of S_{tor} by WMS is based on potential energy, the qualitative trends of S_{tor} they obtained reflects trends in potential energy barriers. In fact, the entropy trend may be the opposite of that obtained by WMS, as exemplified by the comparison of the torsional entropy of ethane and butane.

A referee pointed out that in most of the examples of interest in organic synthesis, in drug design, in molecular recognition, in molecular self-assembly, etc., the restriction of internal rotations is only partial. He concluded that in these cases the final state could be described by a classical model, and therefore the model of WMS would be roughly correct.

While there is little doubt that complete or almost complete restriction can only occur in a limited number of cases, such as cyclizations leading to small ring compounds, it is also obvious that partial restriction is not univocally defined since the extent of restriction can vary from negligible to complete. Thus the WMS method cannot provide a satisfactory answer to the problem of partial restriction. In fact evaluation of the entropy of partial restriction, as well as choice of the appropriate method(s) for such evaluation, require a precise knowledge of the torsional potential energy curve not only of the initial state but also of the final state. In the WMS

method the final state is classical and characterized by $S(Q_V) = 0$. If one assumes a potential of the form of eq 6, it is found that $S(Q_V) = 0$ when $V_0/RT \sim 35$ (for higher V_0/RT values, $S(Q_V) < 0$). Introducing this value in eq 9, one observes that the classical approximation is acceptable if $1/Q_f < 0.18$.[24] Thus the WMS method provides a value of the entropy loss which is meaningful only if $1/Q_f < 0.18$ and if the final state has a barrier of ~ 87 kJ mol^{-1} at room temperature, a condition which is too singular to be of any general meaning. Note that if $1/Q_f > 0.18$, absurd results can be obtained. For example, in the case of ethane ($1/Q_f = 0.377$ at 298.15 K) a rapid calculation shows that $S(Q_T) = S(Q_f) - R \ln(2\pi) = -3.01$ J mol^{-1} K^{-1}. Since $S(Q_V) = 9.7_5$ J mol^{-1} K^{-1} (vide supra), the total entropy of rotation of the initial state calculated by the classical model is $S(Q_T) + S(Q_V) = 6.74$ J mol^{-1} K^{-1}, a value not too far from that calculated by the tables of Pitzer and Gwinn (7.0 J mol^{-1} K^{-1}). However for the final state, the total entropy of rotation, being equal to $S(Q_T)$, would be negative, a clearly unrealistic result. In other words $S(Q_V)$ can be greater than the total entropy, and use of the WMS method would lead to an entropy loss that exceeds the total entropy present in the rotation initially, a clear impossibility.

A final point regards the entries 4, 7, 10 of Table 2 in ref 1, which report values of S_{tor} for "torsions" about the ethynyl group (a linear group) in 1-butyne, butadiyne, and butenyne, respectively. While in the cases of 1-butyne and butenyne such motion is in fact rotation of the *whole molecule* about the axis defined by the ethynyl group, in the case of butadiyne there is not even a degree of freedom associated to such pseudomotion. No matter how these values of S_{tor} have been calculated they are certainly meaningless.

Conclusion

The WMS model is based on the assumption that only the potential energy component of the partition function for a hindered rotation undergoes changes upon restriction of torsional motion, whereas the kinetic energy component remains constant. In the present comment it is remarked that complete restriction (freezing) of a hindered rotation consists in transforming it into a torsional vibration having a frequency higher than about 1000 cm^{-1}, which has a negligible entropic content. Thus *all* the entropy that is present in the rotation initially is lost upon freezing, and not *only* the potential energy component.

Admittedly, complete or almost complete restriction can only occur in a limited number of cases, such as cyclizations leading to small ring compounds; however, knowledge of the entropy of freezing is important because it sets the upper limit for the possible loss of entropy upon restriction of torsional motion which, in most cases, is only partial.

(19) According to note 45 of ref 1, Pitzer (ref 18), and Person and Pimentel (ref 17), would have reported an entropy value of 11.97 and 12.35 J mol^{-1} K^{-1}, respectively, for an internal rotation in an aliphatic chain. In fact both Pitzer, and Person and Pimentel, reported tables of the functions $-(F_T° - H_0°)/T$ and $(H_T° - H_0°)/T$ whose values at 298.15 K are 11.97 and 6.57 J mol^{-1} K^{-1} in the case of Pitzer, and 12.35 and 6.58 J mol^{-1} K^{-1} in the case of Person and Pimentel. The entropy value, $S_T°$, is given by the *sum* of the two functions. It is evident that WMS erroneously considered the first function as equivalent to $S_T°$.

(20) O'Neal, H. E.; Benson, S. W. *J. Chem. Eng. Data* **1970**, *15*, 266−276.

(21) (a) Page, M. I.; Jencks, W. P. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1678−1683. (b) Page, M. I. *Chem. Soc. Rev.* **1973**, *2*, 295−323.

(22) In note 25 of ref 1, it is stated that in the work of Jencks and Page (ref 21a), the kinetic energy component of torsional entropy is ignored. This affirmation of WMS originates from the same misconception that led them to formulate eqs 10 and 11.

(23) Mandolini, L. *Adv. Phys. Org. Chem.* **1986**, *22*, 1−111; p 81.

(24) Although eq 9 has been obtained in the range of V_0/RT [0, 20] it is expected to work also for relatively higher V_0/RT values such as 35. Comparison with entropies obtain by the quantum harmonic oscillator model[12] would confirm this conclusion.