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2

First Principles Prediction of Thermodynamic Properties

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1. Introduction

The determination of the molecular structure is undoubtedly an important issue in chemistry. The knowledge of the tridimensional structure allows the understanding and prediction of the chemical-physics properties and the potential applications of the resulting material. Nevertheless, even for a pure substance, the structure and measured properties reflect the behavior of many distinct geometries (conformers) averaged by the Boltzmann distribution. In general, for flexible molecules, several conformers can be found and the analysis of the physical and chemical properties of these isomers is known as *conformational analysis* (Eliel, 1965). In most of the cases, the conformational processes are associated with small rotational barriers around single bonds, and this fact often leads to mixtures, in which many conformations may exist in equilibrium (Franklin & Feltkamp, 1965). Therefore, the determination of temperature-dependent conformational population is very much welcomed in conformational analysis studies carried out by both experimentalists and theoreticians.

There is a common interest in finding an efficient solution to the problem of determining conformers for large organic molecules. Experimentally, nuclear magnetic resonance (NMR) spectroscopy is considered today to be one of the best methods available for conformational analysis (Franklin & Feltkamp, 1965). Besides NMR, other physical methods, including infrared (IR) spectroscopy (Klaeboe, 1995) and gas phase electron diffraction (ED) experiments (De Almeida, 2000), have been employed in an attempt to determine the geometries and relative energies of conformers. Experimental studies conducted in the gas and condensed phases under a given temperature can yield information on structural parameters and conformational populations, and so Gibbs free energy difference values. On the other side, theoretical calculations employing standard quantum chemical methods can be performed in the search for stationary points on the potential energy surface (PES) enabling the determination of equilibrium geometries, relative energies, spectroscopic and thermodynamic properties of minimum energy and transition state structures (Dos Santos &

De Almeida, 1995; Dos Santos, Taylor-Gomes, De Almeida, 1995; Dos Santos, O´Malley & De Almeida, 1995; Dos Santos, De Almeida & Zerner, 1998; Dos Santos et al., 1998; Rocha et al., 1998; Dos Santos, Rocha & De Almeida, 2002; Anconi et al., 2006; Ferreira, De Almeida & Dos Santos, 2007; Franco et al., 2007, 2008). As a considerable amount of experimental and theoretical work has been already reported addressing the conformational analysis, an assessment of the performance of distinct theoretical approaches for predicting the conformational population as a function of the temperature can be made. In this Chapter we discuss theoretical approaches used for the calculation of thermodynamic quantities, with particular attention paid to the role played by the *ab initio* level of theory and an assessment of the performance of the standard statistical thermodynamics formalism for the evaluation of the entropy contribution to the Gibbs free energy for large molecular systems. The next Sections include the theoretical backgrounds with emphasis in the statistical thermodynamics formalism and some case studies focused on conformational analysis, which we consider as good benchmarks for setting up the methodology due to the low energy change involved in such processes. We believe this contribution will be useful to illustrate most of the essential ideas on first principle calculations of thermodynamic properties generalizing the formalism to handle more complicated situations.

2. Theoretical background

Ab initio quantum mechanical methods have been broadly used for prediction of thermodynamic properties of chemicals and chemical processes with the aid of the well established statistical thermodynamics formalism. The final quantities, namely internal energy (E_{int}), enthalpy (H), entropy (S), Gibbs free energy (G), etc., are actually calculated from *ab initio* data for a single and isolate molecule using the set of quantum states available. These include electronic (normally the ground state), translational (ideal gas and particle in a box model), rotational (rigid-rotor) and vibrational (harmonic oscillator) states, which are the basis for construction of the molecular partition functions (Q). The Gibbs free energy is the primary property in thermodynamics. From the first principle methods it can be calculated by adding two energy quantities (Eq. 1)

$$\Delta G = \Delta E_{ele-nuc} + \Delta G_T \tag{1}$$

where the first term on the right side is the total energy difference within the Born-Oppenheimer approximation (electronic-nuclear attraction, electronic-electronic repulsion plus nuclear-nuclear repulsion potential energy terms) obtained by solving the time-independent Schrödinger equation and the second term is the temperature-pressure dependent thermal correction to the Gibbs free energy, which accounts for enthalpy and entropy contributions (Eq. 2).

$$\Delta G_T = \Delta H_T - T\Delta S \tag{2}$$

where ΔH_T is the thermal correction to enthalpy. In analogy to Eq. (1) we can write the relative enthalpy as Eq. (3).

$$\Delta H = \Delta E_{ele-nuc} + \Delta H_T \tag{3}$$

The $\Delta E_{ele-nuc}$ depends essentially on the approach used to solve the electronic time-independent Schrödinger equation (Eq. 4) that includes the simplest Hartree-Fock (HF)

level up to the very sophisticated *post*-HF Coupled-Cluster approximation (CC). We define $E_{ele-nuc}$ as a sum of the pure electronic energy (E_{ele}) given by Eq. (4) and the nuclear-nuclear repulsion energy (V_{NN}) at equilibrium positions on the PES, in the light of the Born-Oppenheimer approximation ($E_{ele-nuc} = E_{ele} + V_{NN}$).

$$\widehat{H}\Psi_{ele} = E_{ele}\Psi_{ele} \tag{4}$$

All these methods are based on solid quantum mechanics foundations, thus it might be thought that the use of the state of the art CC with single, double and perturbative triple excitations (CCSD(T)), employing a sufficient large basis set (triple-zeta quality), for the calculation of the quantum mechanical terms necessary for the evaluation of the Gibbs free energy would always lead to a perfect agreement with experimental findings. Our recent theoretical results from conformational population studies of cycloalkanes (Rocha et al., 1998; Dos Santos, Rocha & De Almeida, 2002; Anconi et al., 2006; Ferreira, De Almeida & Dos Santos, 2007; Franco et al., 2007) and small substituted alkanes (Franco et al., 2008), where highly correlated *ab initio* calculations are computational affordable, showed that this is not always the case.

According to the standard statistical thermodynamics the partition function of the molecular system is given by Eq. (5), where ε_i is the energy of the distinct allowed quantum states, k the Boltzmann constant and T the absolute temperature (Mcquarrie, 1973). The full molecular partition function ($Q^{tot}(T)$) can be written as a product of electronic, translational, rotational and vibrational contributions (Eq. 6). We found that the vibrational partition function (Eqs. 7 and 8), derived in the light of the statistical thermodynamics approach, is significantly affected by the presence of low frequency vibrational modes (less than approx. 625 cm^{-1} at room temperature) leading to considerable deviation between theoretical and experimental predictions for thermodynamic properties. It is important to remind that a low frequency mode is defined as one for which more than 5% of an assembly of molecules are likely to exist in excited vibrational states at room temperature. In other units, this corresponds to about 625 cm^{-1}, 1.9×10^{13} Hz, or a vibrational temperature ($\theta_K = \frac{h\nu_K}{k_B}$, for the kth vibrational mode) of 900 K.

$$Q(T) = \sum_i e^{-\varepsilon_i/kT} \tag{5}$$

$$Q^{tot}(T) = Q_{ele} \times Q_{trans} \times Q_{rot} \times Q_{vib} \tag{6}$$

$$Q_{vib}^{\nu}(T) = \frac{e^{-h\nu/2kT}}{1-e^{-h\nu/kT}} \tag{7}$$

$$Q_{vib} = \prod_{j=1}^{Nlow} Q_{vib}^{\nu_j} \cdot \prod_{j=Nlow+1}^{3N-6} Q_{vib}^{\nu_j} \tag{8a}$$

$$Q_{vib} = Q_{vib}^{NHO} \cdot Q_{vib}^{HO} \tag{8b}$$

In Eq. (8a) the first product on the right side accounts for the contribution due to the low frequency vibrational modes (*Nlow*), which are not true harmonic oscillators. So they can be treated separately as indicated in Eq. (8b). As a first assumption we can exclude these frequencies (*Nlow* modes) from vibrational partition function, which is equivalent to set up the first product in Eq. 8a to unity (hereafter called HO approach). This approach was firstly introduced in our paper on cyclooctane (Dos Santos, Rocha & De Almeida, 2002).

According to the statistical thermodynamics formalism (see Mcquarrie, 1973) the vibrational contribution to internal energy and entropy are given by Eqs. (9) and (10), respectively, with similar equations holding for the electronic, translational and rotational terms ($Q_{ele}, Q_{trans}, Q_{rot}$). Assuming that the first electronic excitation energy is much greater than kT, and so the first and higher excited states can be considered to be inaccessible, the electronic partition function is simply the electronic spin multiplicity of the molecule ($Q_{ele} = 2S + 1$), with the energy of the electronic ground state set to zero. The translational and rotational partition functions are given by the particle in a box (Q_{trans}) and rigid rotor (Q_{rot}) models respectively (Mcquarrie, 1973).

$$E_{int,vib} = RT^2 \left(\frac{\partial lnQ_{vib}}{\partial T}\right)_V \tag{9}$$

$$S_{vib} = R + RlnQ_{vib} + RT \left(\frac{\partial lnQ_{vib}}{\partial T}\right)_V \tag{10}$$

In the HO approach introduced previously (Dos Santos, Rocha & De Almeida, 2002), the Q_{vib}^{NHO} partition function is made equal to unity, and so, following Eqs. (8b), (9) and (10), the low frequency modes do not make a contribution to the evaluation of thermodynamic properties (null value). It is also possible, for very simple molecules, as will be shown latter, to use other empirical approaches such as hindered rotor analysis and including anharmonic treatment of the low frequency modes (see for example Truhlar, 1991; Ayala & Schlegel, 1998). The way that the low frequency modes are treated is crucial for the correct evaluation of conformational population. For large cycloalkanes, other macrocycles and supramolecular systems there will be a great number of low frequency modes and so the uncertainty in the theoretical determination of relative values of Gibbs free energy tends to naturally increase.

It is opportune to clarify the notation we have been using for thermodynamic quantities, which may differ from that commonly used in many textbooks on thermodynamics. In the way that the vibrational partition function is calculated using the Gaussian package, which we used to perform quantum chemical calculations, the zero of energy is choosen as the bottom of the internuclear potential well. Then, the vibratonal partition function, for the specific frequency ν, is given by Eq. (7) and the zero-point energy (ZPE) contribution ($h\nu/2kT$ or ZPE/kT) is added to the internal energy, which we called E_{int}. In addition, the thermal energy correction to enthalpy (ΔH_T) within the ideal gas model is given by $E_{int} + nRT$. In conformation analysis studies for a given process A →B, the nRT term cancelled out and so the thermal correction to enthalpy is just ΔE_{int} ($\Delta H_T = \Delta E_{int}$) . The thermal correction to Gibbs free energy (named here ΔG_T) is given by Eq. (2).

In the next Sections we will present theoretical thermodynamic quantity results for substituted alkanes and cycloalkanes, where experimental conformational population data are available, which can illustrate the performance of theoretical approaches available for the calculation of thermodynamic properties.

3. Conformational analysis of 1,2-substituted alkanes

There have been a considerable number of investigations on substituted alkanes such as 1,2-dichlroethane (Ainsworth & Karle, 1952; Orville-Thomas, 1974; Youssoufi, Herman & Lievin, 1998; Roberts, 2006; Freitas & Rittner, 2007) and 1,2-difluoroethane (Orville-Thomas,

1974; Hirano et al., 1986; Wiberg & Murcko, 1987; Durig et al., 1992; Roberts, 2006; Freitas & Rittner, 2007) motivated by the interest in its restricted internal rotation. The recent literature for the simple non-substituted ethane molecule also shows that the reason for the rotational barrier leading to the experimentally observed staggered structure (Pophristic & Goodman, 2001; Bickelhaupt & Baerends, 2003) has also been investigated. It is well known that for 1,2-dichloroethane the *anti* form predominates over the *gauche* conformer. However the opposite is observed for the 1,2-difluoroethane, where both experimental and theoretical investigations have shown that this molecule prefer the *gauche* conformation, what has been successfully rationalized in terms of a hyperconjugation model (Goodman, Gu & Pophristic, 2005). So, in the case of the 1,2-difluoroethane molecule, the stability of the *gauche* conformation has been attributed to the high electronegative character of the fluorine atom denominated the *gauche effect*, where the equilibrium geometry is a result of charge transfer from C-H electron to the C-F* antibonds (Goodman & Sauers, 2005). Investigation of the far IR (50-370 cm^{-1}) and low frequency Raman (70-300 cm^{-1}) spectra (Durig et al., 1992) of the gas phase sample of 1,2-difluoroethane showed that the *gauche* conformer is 0.81±0.13 kcal mol^{-1} more stable than the *anti* form, and it has been one of the most discussed case of intramolecular interaction over the past decades.

The very simple ethane molecule has called the attention of many researchers with a number of work reported addressing restricted internal rotation (Kemp & Pitzer, 1936; Ainsworth & Karle, 1952; Pitzer, 1983; Pophristic & Goodman, 2001; Bickelhaupt & Baerends, 2003; Goodman, Gu & Pophristic, 2005). The experimental gas phase spectroscopic and thermodynamic data available for ethane and ethane substituted molecules provide useful information to assess the capability of available theoretical methods used to calculate temperature-dependent macroscopic properties. In order to investigate the performance of theoretical approaches for predicting relative gas phase conformational population values, as compared to observed experimental data, two distinct points must be considered: the adequacy of the theoretical model employed, which is reflected in the pertinence of the mathematical equations developed, and the quality of the calculated energy values used to feed the mathematical functions to produce numerical values for the population ratio, which is dictated by the *ab initio* level of theory employed. Regarding the calculation of Gibbs conformational population, on one side we have the statistical thermodynamic formalism which makes use of molecular partition functions based on Boltzmann distributions and also additional corrections for hindered rotation through the use of empirical formulae, and on the other side the quantum mechanical methods available for the resolution of the time independent Schrödinger equation for an isolated molecule in the vacuum, which produce the various energy values (electronic, rotational, vibrational) and structural data to feed the thermodynamic partition functions. At this point the validity of the theoretical approaches is attested by comparison with experimental conformational population data within experimental uncertainties.

The theoretical methods available for the determination of thermodynamic properties are based on quantum mechanics and statistical thermodynamics formalism and are quite sound, from a methodological point of view. We can reach the state of the art of a quantum mechanical calculation by using a highly correlated *ab initio* method and a basis set close to completeness, and therefore any disagreement with experimentally observed quantities cannot be blamed only on the level of theory used to calculated geometrical parameters, vibrational frequencies and relative electronic plus nuclear-nuclear repulsion energy values ($\Delta E_{ele-nuc}$). However, the evaluation of thermal corrections (ΔG_T) that lead to the

calculation of relative ΔG values (Eq. 1) for a given temperature may not be improved in the same manner as $\Delta E_{ele-nuc}$, which is dictated by the level of electron correlation and size of basis set. The thermal correction is calculated using the statistical thermodynamics partition functions with the vibrational (Q_{vib}) and rotation (Q_{rot}) contributions playing a key role. The rotation and vibrational partition functions are commonly evaluated in the light of the rigid rotor (RR) and harmonic oscillator (HO) approximation, usually denominated RR-HO partition function. To account for deviation from the RR-HO approximation centrifugal distortion effect and anharmonicity correction must be addressed and this is not a simple matter for large molecules. We have observed in our recent studies on substituted alkanes (Franco et al., 2008) that the vibrational contribution to the thermal correction given by Q_{vib} (see Eq. 7) plays a major role for the evaluation of relative ΔG values, and so we have concentrated our attention on the analysis of effect of the low frequency modes on the calculation of the vibrational thermal correction given by Eq. (11) (remember we use $\Delta E_{int} = \Delta H_T$ for conformational interconversion processes). As the internal energy and entropy quantities are given by a logarithmic function (see eqs. 9 and 10), the total thermal correction can be written as a sum of four contributions according to Eq. (12), where only the last term on the right side of Eq. (12) affects significantly the calculation of relative Gibbs free energies and so conformational population values.

$$\Delta G_{T,vib} = \Delta E_{int,vib} - T\Delta S_{vib} \tag{11}$$

$$\Delta G_T = \Delta G_{T,ele} + \Delta G_{T,trans} + \Delta G_{T,rot} + \Delta G_{T,vib} \tag{12}$$

A treatment of low frequency vibrational modes, which are not true vibrations, as hindered rotations, is well known to be required to describe the thermodynamics of ethane and ethane substituted molecules. In (Ayala & Schlegel, 1998) a treatment of low frequency modes as internal hindered rotation is described in details, with an automatic procedure for the identification of low frequency modes as hindered rotor, requiring no user intervention (implemented in the Gaussian® computer code), being reported. Following early works of Pitzer et al. (Pitzer & Gwinn, 1942) tabulating thermodynamic functions, formulas became available to interpolate the partition function between that of a free rotor, hindered rotor and harmonic oscillators (Pitzer & Gwinn, 1942; Li & Pitzer, 1956; Truhlar, 1991; Mcclurg, Flagan & Goddard, 1997), with the approximation by Truhlar (Truhlar, 1991) being used in many studies in recent years. In (Ayala & Schlegel, 1998) a modified approximation to the hindered rotor partition function for the ith low frequency mode (named here $Q_i^{Hind-Rot}$) was given. These formulas (see (Pitzer & Gwinn, 1942) are for one normal vibrational mode involving a single rotating group with clearly defined moment of inertia. The thermal corrections to enthalpy and Gibbs free energy, including hindered rotation and anharmonic correction to vibrational frequencies are calculated according to Eqs. (13) and (14) below, using the Mϕller-Plesset second-order perturbation theory (MP2) and good quality basis sets. The symbols *Hind-Rot* and *Anh* indicate the use of hindered rotation and anharmonicity correction to vibrational frequencies treatments respectively, to account for deviations from the RR-HO partition function. For more details of mathematical treatments see a recent review by Ellingson et al. (Ellingson et al., 2006).

$$\Delta E_{int}^{Hind-Rot-Anh} = \Delta E_{int} + \Delta E_{int}^{Hind-Rot} + \Delta E_{int}^{Hind-Anh} \tag{13}$$

$$\Delta G_T^{Hind-Rot-Anh} = \Delta G_T + \Delta G_T^{Hind-Rot} + \Delta G_T^{Hind-Anh} \tag{14}$$

Table 1 reports the calculation of absolute entropy for ethane at room temperature, using the MP2 level of theory and the 6-311++G(3df,3pd) triple zeta quality basis set, with the aid of the standard statistical thermodynamics formalism with the inclusion of a treatment of the hindered-rotation effects and anharmonicity correction to vibrational frequencies. From the results reported in Table 1 it can be seen that the combination of anharmonic correction to vibrational frequencies and a hindered rotor treatment of the lowest-frequency modes provides a perfect description of the entropy of ethane at room temperature, when a large basis set is used (at least of triple zeta quality) with a MP2 calculation. The deviation from the experimental value is only 0.3% which is within the experimental uncertainty of ±0.19 cal mol^{-1} K^{-1}. The percent error for the aug-cc-pVTZ basis set is only 0.2% (Franco et al., 2008). Therefore, for the ethane molecule, the approach given by Eqs. (13) and (14) works very well.

	S [a]	S^{HO} [b]	S^{Anh} [c]	$S^{Hind-Ror}$ [d]	$S^{Hind-Rot-Anh}$ [e]
Calculated Entropy	54.29 {1.0%} [f]	52.99 {3.4%} [f]	54.45 {0.7%} [f]	54.54 {0.6%} [f]	54.70 {0.3%} [f]
Expt. [g]					54.85±0.19[g]

[a] $S = S_{trans} + S_{rot} + S_{vib}$ (S_{trans} = 36.13 and S_{rot} = 16.26 cal mol^{-1} K^{-1}). 1 cal = 4.184 J. [b]The low frequency mode was excluded from the evaluation of the vibrational partition function for the calculation of the absolute entropy (HO approach) so, 3N-7 normal modes were used. The low frequency contribution to entropy (S_{vib}^{NHO}) is 1.30 cal mol^{-1} K^{-1}. [c]Absolute entropy value calculated with the inclusion of anharmonicity correction. [d]Absolute entropy value calculated with the inclusion of hindered internal rotation correction. [e]Absolute entropy value calculated with the inclusion of anharmonicity and hindered internal rotation corrections for the evaluation of the vibrational partition function. Contributions to the total entropy value: S_{vib}^{HO} = 0.60; S_{vib}^{NHO} = 1.30; $S_{vib}^{Hind-Rot}$ = 0.25; S_{vib}^{Anh} = 0.16 cal mol^{-1} K^{-1}. $S_{vib}^{Hind-Rot-Anh} = S_{vib}^{HO} + S_{vib}^{NHO} + S_{vib}^{Hind-Rot} + S_{vib}^{Anh}$ = 2.31 cal mol^{-1} K^{-1}. [f]Percent error relative to the experimental entropy value obtained at 298.15 K from (Kemp & Pitzer, 1937). The corresponding error for the TS value are only 0.04 kcal mol^{-1}. [g]Experimental entropy value from (Kemp & Pitzer, 1937).

Table 1. MP2/6-311++G(3df,3pd) absolute entropy (cal mol^{-1} K^{-1}) of the ethane molecule in the staggered form (T = 298 K, p = 1 atm) calculated using standard statistical thermodynamics partition function (particle in a box, rigid rotor and harmonic oscillator approximations for translational, rotational and vibrational contributions) including all 3N-6 vibrational modes as harmonic oscillators.

MP2 thermal quantities (ΔE_{int} and ΔG_T) results using various basis sets for the *anti→gauche* process for 1,2-difluorethane (Figure 1) are shown in Figure 2 (a similar behavior was found for 1,2-dichloroethane).

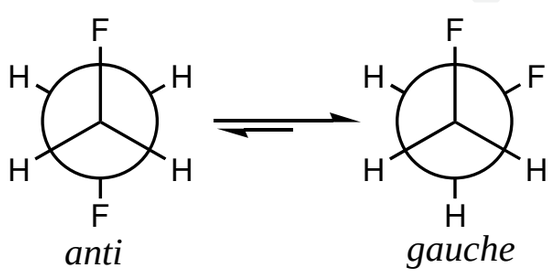


Fig. 1. Schematic representation of the *anti→gauche* process for the 1,2-difluorethane molecule.

It can be seen from Figure 2 that the thermal corrections reached nearly unchanged values within 0.02 kcal mol^{-1} at the MP2/6-311++G(3df,3pd) level of theory, a variation that would cause a change on the calculated conformational population of less than 1%. Figure 3 shows $\Delta E_{ele-nuc}$ results for 1,2-difluorethane (a similar pattern was obtained for 1,2-dicloroethane), where the effect of the electronic correlation and size of the basis set on relative energy values can be analyzed. It can be seen that the MP4(SDTQ) and CCSD(T) relative energies for the *anti→gauche* process agree within less than 0.05 kcal mol^{-1}, showing a welcome smooth behavior of the energy values as a function of the level of theory and basis set quality. We may say that the MP4(SDTQ) and CCSD(T) conformational energies might be trusted with a rough uncertainty estimated at ±0.05 kcal mol^{-1} based on the pattern shown in Figure 3, with a corresponding uncertainty in the conformational population of approximately 1%. The reported uncertainties for experimental conformational populations are in the range of ±2–5%, and the uncertainty value for experimental enthalpy determination is within ±0.10–0.19 kcal mol^{-1}. Therefore, we are confident in using these *ab initio* data to analyze the performance of the theoretical models for calculating thermal corrections through the evaluation of molecular partition functions, making use of the statistical thermodynamics formalism and, therefore, enthalpy and Gibbs free-energy values, leading to the theoretical determination of conformational population ratios.

The Gibbs population results for the *anti→gauche* processes (see Figure 1) for 1,2-difluoroethane and 1,2-dichloroethane at 25°C are reported in Table 2. It can be seen that the effect of the anharmonic correction to the vibrational frequencies on the thermal energies is quite small (±0.01 kcal mol^{-1}) and so it can be neglected; therefore, only the treatment of the low-frequency modes need to be considered. It is important to make it clear that the anharmonicity effect was not included explicitly in the vibrational partition function, which can easily be done for diatomic molecules (Mcquarrie, 1973); however, much more work is required for polyatomic molecules. In the present case, the harmonic oscillator functional dependence was used for the vibrational partition function, but the anharmonic frequencies are utilized instead of harmonic values. As far as enthalpy calculations are concerned, it was found that the *ab initio* and experimental enthalpy values for the *anti→gauche* process exhibit a very fair agreement, for both 1,2-dichloroethane and 1,2-difluorethane, independent of the way that the low-frequency modes are treated (see Table 3). In other words, the internal energy contribution is not so sensitive to the model used to treat the low-frequency modes in the calculation of relative enthalpy values, with the $\Delta E_{ele-nuc}$ contribution being of major relevance (Franco et al., 2008).

When the agreement between theoretical and experimental populations is analyzed, an assessment of the performance of the hindered-rotor approach can be made. From Table 2, the effectiveness of the hindered-rotor approach to describe the 1,2-dichloroethane species is promptly seen, leading to a good agreement with gas-phase electron diffraction conformational population data. The simple procedure of neglecting the low-frequency modes (three modes at room temperature) in the evaluation of the vibrational partition function, which may be considered as a rough but simple approximation also works well for 1,2-dichloroethane. For 1,2-difluorethane, a satisfactory agreement with experimental conformational population data was not obtained. An interesting feature that can be seen from Table 2 is the fact that the procedure of treating the lowest-frequency modes as a hindered rotor leads to a very small correction, compared to the corresponding value obtained for 1,2-dichloroethane, providing virtually the same conformational population as the consideration of all 3N-6 modes as harmonic oscillators. So, in this case, the procedure

was useless. The alternative of ignoring the three lowest-frequency modes also does not work well here.

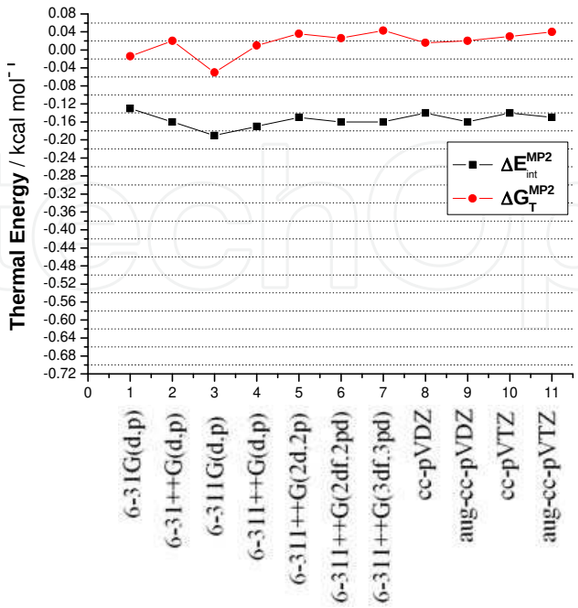


Fig. 2. *Anti→gauche* MP2 thermal energy variation (at room temperature) for 1,2-difluorethane as a function of the basis set quality. The MP2/6-311++G(3df,3pd) and MP2/aug-cc-pVTZ TΔS values (entropic contribution) are respectively -0.20 and -0.19 kcal mol^{-1} (see Eq. 2).

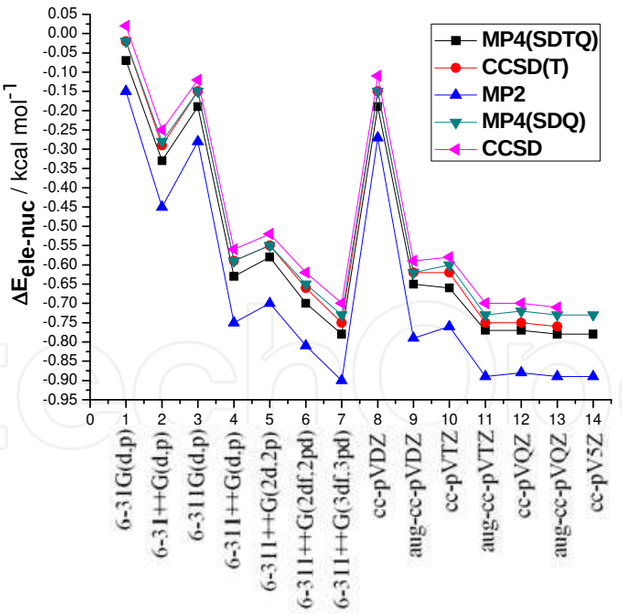


Fig. 3. *Anti→gauche* energy ($\Delta E_{ele-nuc}$ in the vacuum) variation for 1,2-difluorethane as a function of the level of calculation. The CCSD(T)/6-311++G(3df,3pd)//MP2/6-311++G(3df,3pd) and CCSD(T)/aug-cc-pVQZ//MP2/aug-cc-pVTZ relative energy values are respectively -0.75 and -0.76 kcal mol^{-1}. The corresponding MP4(SDTQ) values are respectively -0.78 and -0.78 kcal mol^{-1} (The MP4(SDTQ)/cc-pV5Z//MP2/aug-cc-pVTZ value is -0.78 kcal mol^{-1}).

	1,2-dichloroethane	1,2-difluorethane
$T\Delta S$ [a]	-0.11	-0.17
$T\Delta S^{HO}$ [b]	0.13	0.05
$T\Delta S^{Anh}$ [c]	0.01	-0.003
$T\Delta S^{Hind-Rot}$ [d]	0.40	-0.04
$T\Delta S^{Hint-Rot-Anh}$ [e]	0.41	-0.04
ΔG [% *anti*]	1.30 [90%]	-0.73 [23%]
ΔG^{HO} [b] [% *anti*]	0.95 [83%]	-1.03 [15%]
$\Delta G^{Hint-Rot-Anh}$ [f] [% *anti*]	0.90 [82%]	-0.70 [23%]
[% *anti*] *expt*	[78±5%][g]	[37±5%][h]

[a]The MP2/aug-cc-pVTZ TΔS values for 1,2-dichloroethane and 1,2-difluorethane and are respectively -0.11 and -0.20 kcal mol^{-1} at 25 °C. The room temperature MP2/6-311++G(3df,3pd) rotational entropy ($T\Delta S_{rot}$) contributions are 0.11 and 0.05 kcal mol^{-1} for 1,2-dichloroethane and 1,2-difluorethane, respectively (identical to the MP2/aug-cc-pVTZ values). [b] Calculated using the vibrational partition function evaluated excluding the low frequency normal vibrational modes (three modes at room temperature). [c]Anharmonicity correction evaluated at the MP2/6-311++G(2d,2p) level and room temperature. [d]Internal rotation correction to the MP2/6-311++G(3df,3pd) entropy term ($T\Delta S$) value (one internal rotation was identified for all four species). [e]Anharmonicity and hindered internal rotation corrections. [f]$\Delta G^{Hind-Rot-Anh} = \Delta E_{ele-nuc} + \Delta G_T + \Delta G_T^{Hind-Rot} + \Delta G_T^{Anh}$, with $\Delta G_T = \Delta H_T - T\Delta S$. Value obtained including the anharmonicity and hindered internal rotation correction to calculation of the thermal energy correction (ΔG_T). This should be our best Gibbs free energy value. [g]Experimental value from (Ainsworth & Karle, 1952). See also (Bernstein, 1949). [h]Experimental value from (Durig et al., 1992). There are other two population data obtained from electron diffraction experiment that differ considerably from the more recent reported value in (Durig et al., 1992) based on the vibrational spectroscopy analysis: 9% of the *anti* form from (Fernholt & Kveseth, 1980) at room temperature and 4.0±1.8% at 22 °C from (Friesen & Hedberg, 1980).

Table 2. Temperature-dependent Gibbs population and relative Gibbs free energy (ΔG) values calculated including anharmonicity and hindered-rotation effects on the entropy contribution ($T\Delta S$) to the thermal energy correction (ΔG_T) calculated at the MP2/6-311++G(3df,3pd) level, for the *anti*→*gauche* interconversion process for 1,2-dichloroethane and 1,2-difluorethane. CCSD(T)/6-311++G(3df,3pd)//MP2/6-311++G(3df,3pd) $\Delta E_{ele-nuc}$ values (1.31 and -0.75 kcal mol^{-1} for 1,2-dichloroethane and 1,2-difluorethane, respectively) were used. All values are in kcal mol^{-1}. T = 298.15 K.

In an attempt to better understand the reason for the disagreement between theoretical and experimental gas phase conformational population for 1,2-difluorethane we decided to use the experimental entropy for the *anti*→*gauche* process. It was obtained from the analysis of the vibrational spectral data dependence with temperature reported in (Durig et al., 1992), where by applying the van't Hoff isochore equation, $ln(I_{anti}/I_{gauche}) = \Delta H/RT - \Delta S/R$, with the value in parenthesis being the ration of the intensities of the Raman lines due to the *anti* and *gauche* conformers, the entropy change for the process could be evaluated (assuming that ΔH is not a function of the temperature). The enthalpy is determined through the $ln(I_{anti}/I_{gauche})$ versus $1/T$ plot, where $\Delta H/R$ is the slope of the line. The experimental entropy contribution at room temperature is: $T\Delta S^{Expt}$ = -0.49 kcal mol^{-1}. Our MP2/6-311++G(3df,3pd) best value is -0.17 kcal mol^{-1} (a quite sizeable 65% difference). Using the experimental entropy and our *ab initio* CCSD(T)/6-311++G(3df,3pd) relative energy ($\Delta E_{ele-nuc}$) and MP2/6-311++G(3df,3pd) internal energy (ΔE_{int}) we obtain a room

temperature Gibbs population of 33% of the *anti* form, in good agreement with the experimental value of 37±5%. Therefore, it is quite evident that our calculated entropy for the *anti→gauche* process of 1,2-difluorethane, using the combined quantum mechanical/statistical thermodynamic approach, is in serious error. It is also opportune to emphasize here that, as already pointed out by Ayala and Schlegel (Ayala & Schlegel, 1998), in principle most of the problem resides in the identification of the internal rotation modes. Large molecules can have a large number of low frequency modes which can include not only internal rotations but also large amplitude collective bending motions of atoms. Moreover, some of the low frequency modes can be a mixture of such motions. For large cyclic molecules there are ring torsional modes, and similar to internal rotations ring torsions can cause problems in the evaluation of thermodynamic functions, as will be shown in the next Section.

	1,2-dichloroethane	1,2-difluorethane
ΔH	1.19	-0.90
ΔH^{HO} [a]	1.08	-0.98
$\Delta H^{Hint-Rot-Anh}$ [b]	1.17	-0.93
ΔH^{Expt}	[1.20±0.19][c]	[-0.81±0.13][d]

[a]Calculated using the vibrational partition function evaluated excluding the low frequency normal vibrational modes (three modes at room temperature). [b] $\Delta H^{Hint-Rot-Anh} = \Delta E_{ele-nuc} + \Delta E_{int} + \Delta E_{int}^{Hint-Rot} + \Delta E_{int}^{Anh}$. Value obtained including the anharmonicity and hindered internal rotation correction to calculation of the internal energy correction. The anharmonic correction to internal energy (ΔE_{int}^{Anh}) is -0.01 kcal mol^{-1} for both 1,2-dichloro and 1,2-difluorethane, evaluated at the MP2/6-311++G(2d,2p) level and room temperature. This should be our best enthalpy value. [c]Experimental value from (Bernstein, 1949). [d]Experimental value from (Durig et al., 1992).

Table 3. Enthalpy (ΔH in kcal mol^{-1}) values calculated including anharmonicity and hindered-rotation effects on the internal energy correction (ΔE_{int}) evaluated at the MP2/6-311++G(3df,3pd) level, corresponding to the *anti→gauche* interconversion process for 1,2-dichloroethane and 1,2-difluorethane. CCSD(T)/6-311++G(3df,3pd)//MP2/6-311++G(3df,3pd). $\Delta E_{ele-nuc}$values (1.31 and -0.75 kcal mol^{-1} for 1,2-dichloroethane and 1,2-difluorethane respectively) were used. T = 298.15 K.

It is well known that the vibrational entropy term ($T\Delta S_{vib}$) has a much higher sensibility to the low frequency mode than the internal energy ($\Delta E_{int,vib}$), what can be easily seen from Figure 4 where the variation of the respective thermodynamic functions with the vibrational frequency is shown. $\Delta E_{int,vib}$ is very monotonically dependent on the frequency in the low frequency region, what explain why our calculated enthalpies are in good agreement with the experimental ones. On the contrary, the entropy counterpart is strongly dependent of the frequency, particularly in the region of 0-200 cm^{-1}, therefore, the treatment of low frequency modes definitively has a pronounced effect on the entropy evaluation.

4. Conformational analysis of cycloalkanes

Despite a rather simple carbon–hydrogen cyclic skeleton structure, the cycloalkanes have indeed attracted the interest of several research investigations in the experimental and theoretical fields. These studies are mainly concerned with the conformational analysis as a

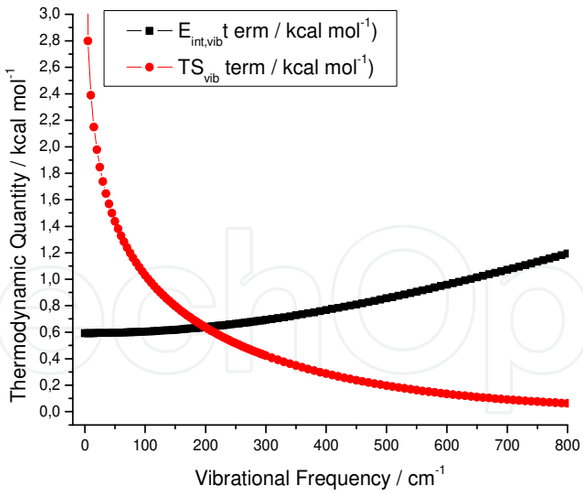


Fig. 4. Thermodynamic energy or internal thermal energy ($E_{int,vib}$) and entropic (TS_{vib}) vibrational contributions (in units of kcal mol-1) represented as a function of the vibrational frequency, calculated with the aid of the statistical thermodynamics formulae, within the harmonic oscillator (HO) approximation (HO vibrational partition function), at room temperature and normal pressure.

function of the temperature and pressure conditions. Electron diffraction experiments have been of great aid to provide population data for cycloalkanes for gas phase samples, as reported for cycloheptane (Dillen & Geise, 1979), cyclooctane (Dorofeeva et al., 1985), cyclodecane (Hilderbrandt, Wieser & Montgomery, 1973) and cyclododecane (Atavin et al., 1989). For solution and solid state samples NMR spectroscopy have provided valuable information for temperature-dependent conformational analysis as given for cyclononane (Anet & Krane, 1980), cyclodecane (Pawar et al., 1998), cycloundecane (Brown, Pawar & Noe, 2003), and cyclododecane (Anet & Rawdah, 1978). In all these experimental investigation a population conformation with an uncertainty of ±5% was reported, and so the preferred conformation for each cycloalkane containing 7 to 12 carbon atoms precisely determined.

In this Section we report a comprehensive conformational analysis for a series of cycloalkanes containing seven to ten carbon atoms (cycloheptane, cyclooctane, cyclononane and cyclodecane) using *ab initio* molecular orbital theory, with the aim to analyze the performance of available theoretical methods to describe large cycloalkanes and also other macrocycles. An investigation of the influence of low frequency vibrational modes in the calculation of thermodynamic properties as a function of temperature, employing standard statistical thermodynamics, was carried on. The main focus of this work is to explore this subject and extend the discussion on the calculation of thermodynamic quantities for other large molecular systems or molecular clusters that are relevant for many areas of chemistry, in particular supramolecular chemistry, and present a challenge for available theoretical methods. Our ultimate goal is a clear understanding of the efficaciousness of standard quantum chemical procedures for the calculation of conformational population of large molecular systems usually containing macrocycle units. This is a relevant academic problem that has not received much attention in the literature so far, which has also important consequences in the application of theoretical methods to solve problems of general and applied chemical interest, such as biological application and material science.

We will present first separate results for each cycloalkane and in the end a global analysis of the cycloalkanes investigated, what can shed some light on the performance of available theoretical methods for the calculation of conformational population of large macrocycles. The mathematical equations necessary for the calculation of relative Gibbs free energy values, with the explicit consideration of low frequency normal modes, were given in Section 2 and we provide now some example to illustrate the application of theoretical methods. In Section 3 we showed the effect of including anharmonicity and hindered-rotation corrections to ΔE_{int} and ΔG_T for 1,2-dichloro and 1,2-difluorethane, which are very simple molecules where available empirical models can be applied. In the case of cycloalkanes we found not appropriate an attempt to include such corrections to the calculation of ΔG_T and our proposal was to separate the vibrational thermal correction in two main contributions given by Eq. (15), where low and high frequency normal modes are included in the NHO and HO terms respectively, since the thermodynamic statistical formalism allowed us to write ΔG_T as a sum of terms.

$$\Delta G_{T,vib} = \Delta G_{T,vib}^{NHO} + \Delta G_{T,vib}^{HO} \tag{15}$$

In this Section we make use of a very simple approach, already introduced in Section 3 of this Chapter named HO approach, that is assuming the vibrational partition function contribution due to the low frequency modes given by equation (8b), Q_{vib}^{NHO}, to be unitary what is equivalent to exclude the corresponding vibrational frequencies from the calculation of the thermal correction, i.e., $\Delta G_{T,vib}^{NHO} = 0$. We will discuss the applicability of this approximation for the series of cycloalkanes where experimental conformational populations are available for comparison. The proposal of another Q_{vib}^{NHO} partition function that is not unitary and so can describe more realistically the effect of the low frequency modes that are no harmonic oscillator is indeed a big challenge in what large molecules are concerned. The most recently reported treatments have been reviewed recently by Ellingson and collaborators (Ellingson et al., 2006) with results for hydrogen peroxide model system presented.

4.1 Cycloheptane

The conformational analysis of cycloheptane has been well documented in the literature (Hendrickson, 1961; Hendrickson, 1967a, 1967b; Dowd et al., 1970; Pickett & Strauss, 1971; Hendrickson et al., 1973; Bocian et al., 1975; Cremer & Pople, 1975; Flapper & Romers, 1975; Brookeman & Rushworth, 1976; Bocian & Strauss, 1977a, 1977b; Flapper et al., 1977; Snyderman et al., 1994; Senderowitz, Guarnieri & Still, 1995; Wiberg, 2003) so it is known that there are five possible distinct conformers being two true minima (twist-chair (TC) and boat (B)) and three first-order transition state (TS) structure, (chair (C), twist-boat (TB) and a third structure named TS3) (Wiberg, 2003). The TC, B and C conformers are depicted in Figure 5. The TC conformer is the global minimum energy structure and is connected to the local minimum B (which is ca. 3 kcal mol^{-1} energetically higher (Wiberg, 2003)) through the TS3 structure, with a reasonable energy barrier of ca. 8 kcal mol^{-1} (Wiberg, 2003). The only experimental conformational data available is from an electron diffraction study (Dillen & Geise, 1979), where a mixture of TC and C conformers was proposed, in order to explain the electron diffraction patterns. In this Section we present a discussion on the performance of the standard quantum chemical methods to describe the structure, energetic and thermodynamic properties of the TC and C conformers of cycloheptane with a special

attention being paid to the role played by the low frequency vibrational modes in the calculation of thermodynamic quantities. By writing the enthalpy and Gibbs free energy as a sum of two independent contributions (see Eqs. (1) and (3)) it is implied that we can use different levels of theory to evaluate each term. Therefore, it is common to use a lower cost computational method for geometry optimization and vibrational frequency calculations, which are need for the determination of ΔG_T, with *post*-HF methods being employed to evaluate the $\Delta E_{ele-nuc}$ counterpart. It is important to assess the performance of theoretical methods for the determination of structural parameters.



(a) TC (b) B (c) C

Fig. 5. MP2 fully optimized structures of the relevant conformers of cycloheptane: (a) TC; (b) B; (c) C. The numbering scheme is included in the Figure 5a.

We report in Table 4 a summary of theoretical and experimental dihedral angles for the global minimum structure located on the PES for cycloheptane (TC), with experimental gas phase electron diffraction data being also quoted for reason of comparison. It can be seen that there is a nice agreement with the MP2 optimized values for the TC structure, with all basis sets employed. It is interesting to see that all fully optimized MP2 dihedral angles agree very well, independent of the basis set used, showing the strength of the MP2 level of theory for structural determination. It can also be seen from Table 4 that DFT (B3LYP functional) torsion angles also agree very well with experimental data. It can be inferred that DFT and MP2 geometrical parameters for cycloalkanes are very satisfactory described and so, the rotational partition function (Q_{rot}), which depends essentially on the structural data through the moment of inertia within the rotor rigid approximation, is also well predicted by DFT and MP2 methods.

	d1 [1,2,3,4]	d2 [2,3,4,5]	d3 [3,4,5,6]	d4 [4,5,6,7]	d5 [5,6,7,1]	d6 [6,7,1,2]	d7 [7,1,2,3]
B3LYP/6-31G(d,p)	38.0	-84.4	70.1	-53.8	70.1	-84.4	38.0
MP2/6-31G(d,p)	39.3	-87.1	70.3	-52.5	70.3	-87.1	39.3
MP2/6-311++G(2d,2p)	39.6	-87.9	70.6	-52.5	70.6	-87.9	39.6
MP2/cc-pVDZ	39.2	-87.0	70.4	-52.8	70.4	-87.0	39.2
MP2/aug-cc-pVDZ	39.7	-88.2	70.6	-52.3	70.6	-88.2	39.7
Expt. [b]	38.3	-86.5	70.8	-52.4	70.8	-86.5	38.3

[a]The labels are defined in Figure 5. [b]Experimental values from (Dillen & Geise, 1979).

Table 4. Dihedral angles[a] (in degrees) calculated for the global minimum TC form of the cycloheptane molecule at different levels of theory.

The energy differences ($\Delta E_{ele-nuc}$) for the conformational interconversion process TC→C, using various methods of calculation, are shown in Tables 5 and 6 (MP4 and CCSD values). It can be seen that, despite the fact of providing reasonable structural data, the B3LYP functional cannot be used for the evaluation energy of differences, compared to MP2, in what cycloheptane is concerned. An extensive investigation of the behavior of other DFT functional is required. Also in Table 5 are internal energy (ΔE_{int}), entropy contribution ($T\Delta S$) and thermal correction (ΔG_T) evaluated at distinct levels of calculation showing a relative good agreement between B3LYP and MP2 results. It can be seen from Table 5 that the vibrational contribution plays the major role in the evaluation of thermal quantities, stressing the importance of using an adequate treatment of the low frequency vibrational modes. It can also be seen from Tables 5 and 6 that the MP2 relative energies are larger than the MP4 and CCSD values, showing the importance of a better description of electron correlation and how the way it is evaluated, and the basis set employed, affects the $\Delta E_{ele-nuc}$ value. The difference between the MP4(SDTQ) and CCSD(T) energy is 0.03 kcal mol^{-1} for both cc-pVDZ and 6-311G(d,p) basis sets. The same result is observed for the smaller 6-31G(d,p) basis set. Therefore, it can be said that the computational more feasible high correlated level of theory, MP4(SDTQ), would lead to a Gibbs conformational population value virtually the same as the CCSD(T) prediction, within the same basis set, and so can be safely used to account for the electronic correlation energy in conformational analysis studies. It can also be seen that the uncertainty in the *post*-HF energy values for the TC→C process is stabilized to less than ~0.1 kcal mol^{-1}. This would lead to a variation of less than 2% in the TC/C conformational population, which is less than the experimental reported uncertainty (Dillen & Geise, 1979). The behavior of the thermal quantities as a function of the level of theory employed can also be analyzed from the results reported in Table 5. It can be seen that the uncertainty in the MP2 entropy and thermal energy values (ΔG_T) is within ~0.05 kcal mol^{-1}, so we can assume that the MP2 thermodynamic quantities reached a converged value within 0.05 kcal mol^{-1}, which would cause a small variation of less than 1% in TC/C conformational population.

Level of theory	$\Delta E_{ele-nuc}$	ΔE_{int}	$T\Delta S$	ΔG_T
B3LYP/6-31G(d,p)	0.69	-0.60	-1.05	0.45
MP2/6-31G(d,p)	1.24 {0.87}[a]	-0.60	-0.92	0.32
MP2/6-31++G(d,p)	1.22 {0.87}[a]	-0.61	-0.92	0.31
MP2/6-311G(d,p)	1.22 {0.83}[a]	-0.57 (-0.60)[b]	-0.93 (-1.01)[c]	0.36 (0.41)[d]
MP2/6-311++G(d,p)	1.21 {0.84}[a]	-0.57	-0.94	0.37
MP2/6-311++G(2d,2p)	1.28 {0.85}[a]	-	-	-
MP2/cc-pVDZ	1.18 {0.87}[a]	-0.58 (0.03)[b]	-0.93 (-0.0002)	0.35 (0.03)[d]
MP2/aug-cc-pVDZ	1.31 {0.89}[a]	-	-	-

[a]Hartree-Fock (HF) contribution to the MP2 fully optimized geometry energy difference. [b]$\Delta E_{int,vib}$. [c]$T\Delta S_{vib}$. [d]$\Delta G_{T,vib}$.

Table 5. Relative total energy ($\Delta E_{ele-nuc}$) and thermodynamic properties calculated for the TC→C equilibrium at T=310 K and 1 atm (values in kcal mol^{-1}).

Single Point Energy Calculations	$\Delta E_{ele-nuc}$ /kcal mol^{-1}
MP4(SDQ)/6-31G(d,p)//MP2/6-31G(d,p)	1.12
MP4(SDTQ)/6-31G(d,p)//MP2/6-31G(d,p)	1.16
CCSD/6-31G(d,p)//MP2/6-31G(d,p)	1.11
CCSD(T)/6-31G(d,p)//MP2/6-31G(d,p)	1.14
MP4(SDQ)/6-311G(d,p)//MP2/6-311G(d,p)	1.10
MP4(SDTQ)/6-311G(d,p)//MP2/6-311G(d,p)	1.15
CCSD/6-311G(d,p)//MP2/6-311G(d,p)	1.08
CCSD(T)/6-311G(d,p)//MP2/6-311G(d,p)	1.12
MP4(SDQ)/cc-pVDZ//MP2/cc-pVDZ	1.07
MP4(SDTQ)/cc-pVDZ//MP2/cc-pVDZ	1.11
CCSD/cc-pVDZ//MP2/cc-pVDZ	1.06
CCSD(T)/cc-pVDZ//MP2/cc-pVDZ	1.08

Table 6. *Post*-HF relative electronic plus nuclear repulsion energy values for cycloheptane: TC→C. The double slash means a single point energy calculation using the geometry optimized at the level indicated after the double slash.

Conformational population values for the TC conformer are given in Figure 6, where the thermodynamic quantities were partitioned into a harmonic contribution (HO) and a low frequency mode part, considered as non-harmonic (NHO), so the total value is a sum of these two contributions. Some of the low frequency modes (eight for TC) may be internal rotations, and so may need to be treated separately, depending on the temperatures and barriers involved. Following the Eq. (15) we can write:

$$\Delta E_{int,vib} = \Delta E_{int,vib}^{NHO} + \Delta E_{int,vib}^{HO} \tag{16}$$

$$T\Delta S_{vib} = T\Delta S_{vib}^{NHO} + T\Delta S_{vib}^{HO} \tag{17}$$

The rotational contribution to the entropic term is also quoted in the caption of Figure 6 (the corresponding contribution for the internal energy $\Delta E_{int,rot}$ is null, as well as the translational term). It can also be seen that the $T\Delta S_{rot}$ term is negligible, and so only the vibrational contributions need to be considered, i.e., $T\Delta S \cong T\Delta S_{vib}$. It can be seen from Figure 6 that the MP4(SDTQ) and CCSD(T) conformational population results agree nicely within 1%, so we are confident that the *ab initio* correlated level of calculation employed is sufficient for the description of the temperature-dependent thermodynamic properties.

The experimental conformational population data for cycloheptane comes from the electron diffraction study, at T = 310 K, reported in (Dillen & Geise, 1979), where a TC/C mixture, with 76±6% of TC, was proposed in order to explain the diffraction intensities. If we take the upper limit of the experimental uncertainty, 82%, this value is still 10% away from Gibbs population conformational value of 92%, evaluated using the 3N-6 vibrational modes. However, ignoring the low frequency modes for the calculation of thermal correction the agreement improves substantially (86–87% of TC/C, compared to the experimental upper limit of 82%). The results reported here provide a substantial support for a separate treatment of the low frequency modes and also stress the role they play for the determination of the conformational population. In order to better understand the effect of the vibrational modes, especially the low frequency ones, on the thermal correction, we present in Figure 7 the MP2/6-311G(d,p) ΔG_T value as a function of the vibrational mode (ν_i).

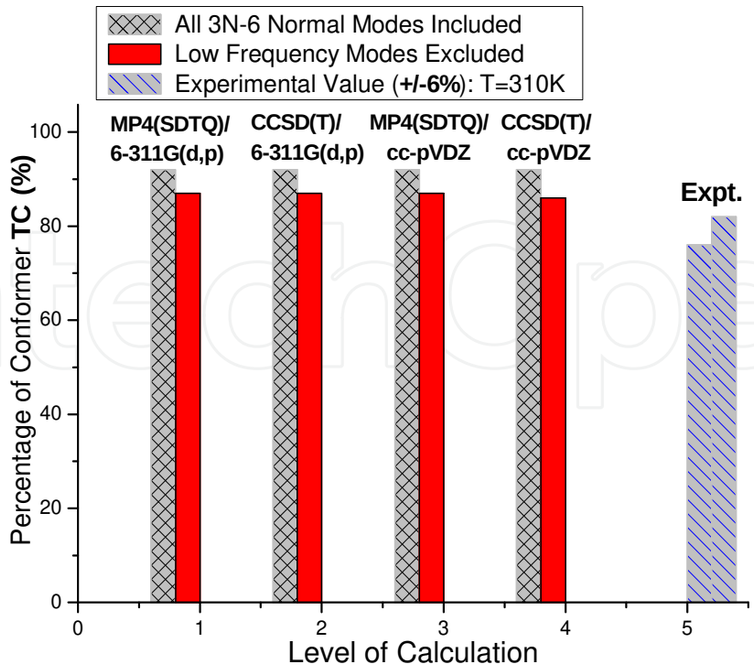


Fig. 6. Conformational population values (TC→C process) for cycloheptane at T = 310 K. Thermal correction ($\Delta G_T = \Delta H_T - T\Delta S$) was evaluated using structural parameters and vibrational frequencies calculated at the MP2/6-311G(d,p) and MP2/cc-pVDZ levels ($\Delta E_{int,trans} = T\Delta S_{trans} = 0$; $\Delta E_{int,rot} = 0$; $T\Delta S_{rot} = 0.0091$ kcal mol^{-1}; $\Delta G_T = 0.41$ *and* $\Delta G_T^{HO} = 0.03$ kcal mol^{-1}: MP2/6-311G(d,p) values).

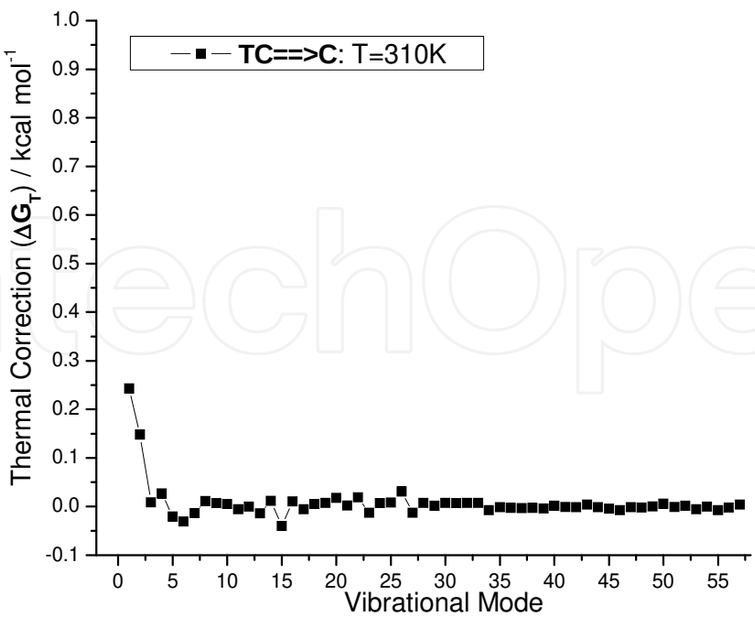


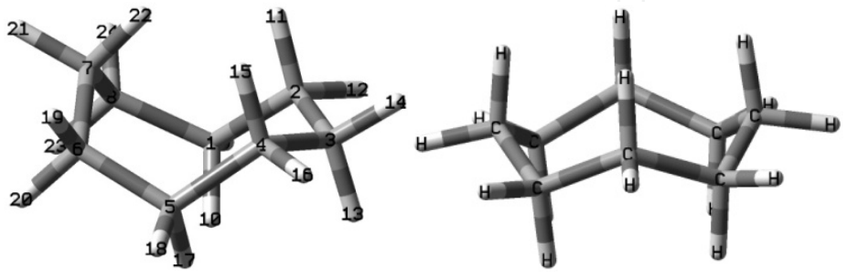
Fig. 7. MP2/6-311G(d,p) thermal correction difference (ΔG_T) as function of each normal mode for the TC→C interconversion process of cycloheptane (T = 310 K).

As can be easily seen from Figure 7, on calculating the thermal correction difference for the TC→C interconversion process the first two vibrational modes make the major contribution accounting for 93% (0.38 kcal mol^{-1}) of the total ΔG_T value of 0.41 kcal mol^{-1}. In the light of these results we decided to re-calculate the thermal correction excluding only the first two low frequency modes of conformers TC and C. The corresponding CCSD(T)/6-311G(d,p)//MP2/6-311G(d,p) and CCSD(T)/cc-pVDZ//MP2/cc-pVDZ TC population values ignoring only the first two normal modes in the evaluation of the vibrational partition function are respectively 86% and 85%, virtually the same as the value obtained excluding all ten low frequency modes from the evaluation of the vibrational partition function (87%) differently by approx. only 1%.
It can be seen that the $\Delta E_{int,vib}^{HO}$ and $\Delta G_{T,vib}^{HO}$ values calculated neglecting all the low frequency modes or only the first two modes are virtually the same, stressing the point that only these two vibrational modes must be treated separately, not as harmonic-oscillators. We then found that a proper treatment of these two low frequency modes for cycloheptane (and also for cyclooctane addressing in the next Section), should yield as a result a thermal correction very close to the values we reported in this work, using the simple procedure of ignoring the first two low frequency modes in the calculation of the thermodynamic quantities.

4.2 Cyclooctane

A considerable amount of experimental and theoretical work has been reported addressing the conformational analysis of the cyclooctane molecule, therefore, an assessment of the performance of distinct theoretical approaches for predicting the conformational population as a function of the temperature can be made. The molecular structure of cyclooctane has been widely discussed since the early 1960s (Eliel et al., 1965). The central point of the discussion is the conformation of the molecule as investigated by a variety of experimental and theoretical methods (see reviews in Anet, 1974; Burkert, 1982 and Brecknell, Raber & Ferguson, 1985; Saunders, 1987; Lipton & Still, 1988; Chang, Guida & Still, 1989; Ferguson et al., 1992; Rocha et al., 1998; De Almeida, 2000). It is important to mention the pioneering work of Hendrickson (Hendrickson, 1964), who reported nine conformations of cyclooctane belonging to three families; CROWN, boat-chair (BC) and boat-boat (BB), concluding that cyclooctane will form a very mobile conformational mixture at ordinary temperature in the gas phase. Almenningen et al. (Almenningen, Bastiansen & Jensen, 1966), in a subsequent electron diffraction study of cyclooctane in the gas phase at 40°C, gave support to Hendrickson's conclusion. At the same time, X-ray studies of cyclooctane derivatives showed that in the crystal the BC conformer is certainly preferred (Dobler, Dunitz & Mugnoli, 1966; Burgi & Dunitz, 1968; Srinivasan & Srikrishnan, 1971). Later, various studies (Anet & Basus, 1973; Meiboom, Hewitt & Luz, 1977; Pakes, Rounds & Strauss, 1981; Dorofeeva et al., 1985, 1990) indicated the exclusive or predominant existence of the BC form of the cyclooctane in the liquid and gas phase.
In this Section we discuss the gas phase conformational analysis of cyclooctane, including the BC and CROWN forms (see Figure 8). We show that the role played by the entropic contribution to the energy balance, which defines the preferable conformer, is very sensitive to the presence of low vibrational modes and the level of calculation used for its determination.
The calculated dihedral angles for the BC form of the cyclooctane molecule, are given in Table 7. There is a good agreement for all *ab initio* and DFT values, being the maximum deviation of ca. 2°. Since the cc-pVDZ basis set is believed to be more appropriated for

correlated *ab initio* calculations we take the MP2/cc-pVDZ as our best level for geometry optimization. Therefore, it can be seen that electron diffraction dihedral angle values reported for the BC conformer agree with our best theoretical result within ca. 2°. The corresponding X-ray data from (Egmond & Romers, 1969) show also a close agreement with our MP2/cc-pVDZ optimized values. The B3LYP dihedral angles are in good agreement with the MP2 ones, being also quite similar to the HF/6-31G(d,p) ones. From the results reported in Table 7 it can be seen that the calculated HF/6-31G(d,p) dihedral angles agree with the MP2/cc-pVDZ optimized values by ca. 1°, showing that, indeed, it is not necessary a high correlated level of theory for a satisfactory prediction of equilibrium structures. A similar behavior was found for cycloheptane as shown in the previous Section.



(a) **BC** (b) **CROWN**

Fig. 8. MP2 fully optimized structures of the BC (a) and CROWN (b) conformers of cyclooctane. The numbering scheme is included in the Figure 8a.

As already mentioned, statistical thermodynamics can be used to calculate temperature-dependent quantities, using equilibrium structures and harmonic frequencies evaluated from quantum mechanical calculations, which in turn are employed in the generation of partition functions. However, the occurrence of low frequency modes that may represent hindered internal rotation, can cause significant errors when the harmonic approximation is used for the calculation of partition functions. For the case of cyclic molecules featuring rings bigger than six-member, as the cyclooctane, the situation is more complicated and treating the internal rotation modes is still a big challenge. Therefore, as discussed in the previous Section, we decided just to remove the low frequency internal rotational modes from the calculations of the partition functions, minimizing the error of using the harmonic approximation for generating vibration partition functions. By comparing the conformational population calculated using vibrational partition functions neglecting the low frequency torsion modes contribution with the experimental predictions we can assess the validity of our assumption.

The results for the thermodynamic analysis, eliminating the low frequency modes from the evaluation of the vibrational partition function, are reported in Table 8, along with the thermal data evaluated considering all 3N-6 harmonic frequency values. It can be seen that the agreement with experiment is much more uniform after the internal rotation modes are excluded from the partition functions for the calculation of the thermal correction. If the low frequency modes are not removed from the thermodynamic analysis a rather non-uniform behavior is predicted.

So, it can be concluded that the low frequency modes, which may be internal rotation modes, have to be treated separately or at least removed. Zero point energy corrections (ΔZPE), internal thermal energy (ΔE_{int}) and entropy term ($-T\Delta S$) contributions to the

thermal energies (ΔG_T) for the BC and CROWN conformers (BC→CROWN interconversion process) for T=298 K are reported in Table 9. The second and third columns of Table 9 contain the values calculated using the harmonic oscillator partition function including all 3N–6 normal modes. In the last two columns of Table 9 are reported the corresponding values obtained by neglecting the low frequency torsion modes in the evaluation of the partition functions. It can be seen that the average deviation for the two sets of calculation (using all 3N-6 frequencies and omitting the low frequency torsion modes), obtained by subtracting the values from columns four and two, and columns five and three, respectively, is ca. 0.2 kcal mol^{-1} for ΔE_{int} and ca. 2 kcal mol^{-1} (MP2 value) for the $T\Delta S$ term. Therefore, the largest effect of the low frequency torsion modes is in the evaluation of the entropy term, which can have a significant effect on the calculation of conformational populations.

	D1	D2	D3	D4
HF/6-31G(d,p)	-65.6	65.6	-99.6	43.6
B3LYP/6-31G(d,p)	-65.2	65.2	-99.6	43.7
B3LYP/6-311G(d,p)	-65.2	65.2	-99.7	43.7
MP2/6-31G(d,p)	-65.2	65.2	-100.7	44.4
MP2/cc-pVDZ	-64.8	64.8	-100.9	44.5
MP2/6-311G(d,p)	-64.8	64.8	-101.1	44.5
Expt. [a]	-63.1	63.1	-98.4	42.0
X-Ray	-70.3 [b] (-60.3)[c]	70.8 [b] (62.6)[c]	-105.9 [b] (-100.0)[c]	46.8 [b] (40.9)[c]
	D5	D6	D7	D8
HF/6-31G(d,p)	63.9	-63.9	-44.6	99.6
B3LYP/6-31G(d,p)	64.1	-64.1	-43.7	99.6
B3LYP/6-311G(d,p)	64.1	-64.1	-43.7	99.7
MP2/6-31G(d,p)	64.9	-64.9	44.3	100.7
MP2/cc-pVDZ	65.1	-65.1	-44.5	100.9
MP2/6-311G(d,p)	65.4	-65.4	-44.5	101.1
Expt. [a]	68.3	-68.3	-42.0	98.4
X-Ray	62.0 [b] (67.5)[c]	-63.0 [b] (-62.2)[c]	-43.4 [b] (-48.2)[c]	100.9[b] (100.6)[c]

[a]Electron diffraction results from (Almenningen, Bastiansen & Jensen, 1966). [b]See (Dobler, Dunitz & Mugnoli, 1966). [c]See (Egmond & Romers, 1969).

Table 7. Dihedral angles (D_i in degrees) for the BC form of the cyclooctane molecule. D1=C_1-C_2-C_3-C_4, D2=C_2-C_3-C_4-C_5, D3=C_3-C_4-C_5-C_6, D4=C_4-C_5-C_6-C_7, D5=C_5-C_6-C_7-C_8, D6=C_6-C_7-C_8-C_1, D7=C_7-C_8-C_1-C_2, D8=C_8-C_1-C_2-C_3.

To ease the analysis of the performance of theoretical methods for calculating population values for cyclooctane, Figure 9 shows DFT, MP2 and MP4(SDTQ) results for the temperature of 332 K, corresponding to the experimental gas phase electron diffraction condition, along with the corresponding experimental data, in the range of 91 to 98% of BC conformer.

T = 298.15 K, p = 1atm	$\Delta E_{ele-nuc}$ [%BC]	ΔG_T	ΔG_T^{HO}	ΔG_T	ΔG_T^{HO}	%BC^{HO} [%BC]
Full Geometry Optimization						
HF/6-31G(d,p)	0.49 [69]	-1.56	-0.18	-1.07	0.31	64 [14]
HF/6-311G(d,p)	0.37 [65]	-1.43	-0.20	-1.06	0.17	58 [14]
B3LYP/6-31G(d,p)	0.32 [63]	-0.82	-0.037	-0.499	0.29	64 [30]
B3LYP/6-311G(d,p)	0.34 [64]	-0.77	-0.01	-0.433	0.33	65 [32]
BLYP/6-31G(d,p)	-0.09 [46]	-0.65	-0.017	-0.740	-0.108	45 [25]
BLYP/6-311G(d,p)	-0.06 [48]	-0.66	-0.03	-0.711	-0.086	46 [23]
MP2/6-31G(d,p)	2.31 [98]	-2.44	-0.20	-0.138	2.11	97 [44]
MP2/cc-pVDZ	2.25 [98]	-2.10	-0.18	0.154	2.07	97 [56]
MP2/6-311G(d,p)	2.59 [99]	-2.45	-0.26	0.143	2.33	98 [96]
Experimental data [+]					1.39/2.20	91-98
Single Point Energy						
CCSD//MP2/cc-pVDZ	1.61 [94]	-2.10	-0.18	-0.49	1.43	92 [30]
MP4//MP2/cc-pVDZ	1.67 [94]	-2.10	-0.18	-0.43	1.49	93 [33]
MP4/cc-pVDZ//HF/631G(d,p)	1.57 [93]	-1.56	-0.18	0.01	1.39	91 [50]

[+]Experimentally, at the temperature of 59°C (332 K), and also room temperature, the boat-chair is either the exclusive or at least the strongly predominant form in the gas phase (See Dorofeeva et al., 1985). ΔE^0 correction is included in ΔE_{int}.

Table 8. Energy differences ($\Delta E_{ele-nuc}$), thermal energies (ΔG_T) and the corresponding values corrected for errors due to internal rotations (ΔG_T^{HO}), Gibbs free energy differences (ΔG) and the values corrected for internal rotation (ΔG^{HO}) and Gibbs populations (values calculated using 3N-6 normal modes as harmonic oscillators are in brackets). The Boltzmann populations are given in brackets in the second column. All energy values are in units of kcal mol^{-1}.

A result that calls our attention is the bad performance of the B3LYP and BLYP DFT functionals for predicting the relative conformational population of the BC and CROWN conformers of cyclooctane. The B3LYP functional (and also calculations with other functional not reported here) produces a very poor result. It can be clearly seen that the problem is in the evaluation of the electronic energy term ($\Delta E_{ele-nuc}$), with the B3LYP thermal correction being at least reasonable. The B3LYP functional underestimates the electronic plus nuclear repulsion energy difference between the CROWN and BC conformers by more than 1 kcal mol^{-1}, which causes a remarkable effect on the conformational population evaluated with the exponential Gibbs free energy. It is hard to say if this is a particular misbehavior for the specific case of cyclooctane molecule or maybe other macrocyclic systems.

It is informative to access explicitly how an uncertainty in the ΔG value can influence the calculation of the conformational population. The relative conformational population corresponding to the BC→CROWN interconversion process is evaluated with the equilibrium constant calculated with the well-known equation given below (Eqs. 18,19), where [BC] and [CROWN] are respectively the concentrations of the BC and CROWN conformers.

	ΔZPE	ΔE_{int}	$-T\Delta S$	ΔE_{int}^{OH}	$-T\Delta S^{HO}$
HF/6-31G(d,p)	-0.57	-0.29	-1.26	-0.13	-0.05
HF/6-311G(d,p)	-0.55	-0.30	-1.13	-0.14	-0.06
HF/6-311++G(d,p)	-0.53	-0.27	-1.18	-0.11	-0.16
MP2/6-31G(d,p)	-0.72	-0.34	-2.11	-0.14	-0.06
MP2/cc-pVDZ	-0.65	-0.31	-1.79	-0.13	-0.05
MP2/6-311G(d,p)	-0.77	-0.40	-2.05	-0.20	-0.06
B3LYP/6-31G(d,p)	-0.28	-0.12	-0.699	0.003	-0.040
B3LYP/6-311G(d,p)	-0.25	-0.10	-0.669	0.03	-0.04

All energy values are in units of kcal mol^{-1}. The values were calculated using the harmonic approximation for the generation of the thermodynamical partition functions for all vibrational modes including the low frequency modes and also, neglecting the low frequency torsion modes (HO approach).

Table 9. Zero-point energy corrections (ΔZPE), internal thermal energy (ΔE_{int}) and entropy term ($-T\Delta S$) contributions to the thermal energies for the BC and CROWN conformers (BC→CROWN interconversion process, T=298 K, p=1atm).

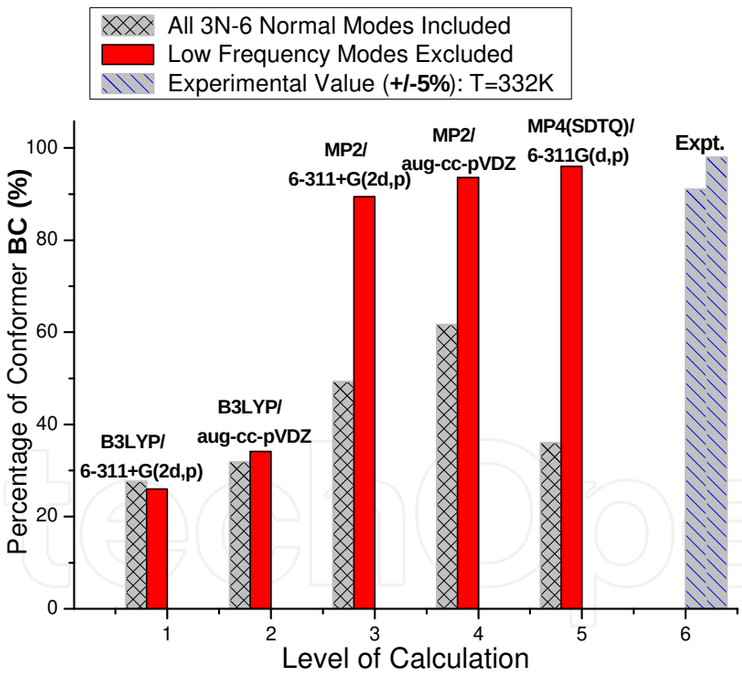


Fig. 9. Population for BC conformer of cyclooctane (BC→CROWN equilibrium process) at T=332K. The MP4(SDTQ) value was calculated using the MP2/6-311G(d,p) thermal correction.

$$\Delta G \quad = G_{CROWN} - G_{BC} \tag{18}$$

$$K_{eq} = \frac{[CROWN]}{[BC]} = \exp(-\frac{\Delta G}{RT}) \tag{19}$$

The BC population can be obtained through the equation below keeping in mind that [BC]+[CROWN]=1.

$$[BC] = \frac{1}{1+\exp(-\frac{\Delta G}{RT})} \tag{20}$$

Let us assume that the Gibbs free energy value is estimated to a precision of ±*d* kcal mol^{-1}. Then the exponential factor in Eq. (20) will be:

$$\exp\left(-\frac{\Delta G}{RT} \pm \frac{d}{RT}\right) = \exp(\pm\frac{d}{RT}) \times \exp\left(-\frac{\Delta G}{RT}\right)$$

Then from Eq. (20),

$$[BC] = \frac{1}{1+f_{\pm}\exp(-\frac{\Delta G}{RT})} \therefore f_{\pm} = \exp(\frac{\pm d}{RT}) \tag{21}$$

Depending on the + or – sign used for *d* (named d_+ or d_-) we have two possibilities for the value of the pre-exponential factor: f_+ or f_-, leading to two distinct conformational populations named, %BC(f_+) and %BC(f_-). From Eq. (21) it can be seen that the accuracy of the %BC value depend on the quality of ΔG and also the uncertainty in its evaluation *d* (or factor, f_+ and f_-). Assuming T = 298.15 K just for comparison, for low values of ΔG a very small uncertainty (less than 0.1 kcal mol^{-1}) is required to produce acceptable variations in the population. For ΔG higher than 3 kcal mol^{-1} an uncertainty of ca. 1 kcal mol^{-1} does not cause significant variations. However, for intermediate values of ΔG as is the case of the cycloalkanes molecule, care is needed and a high correlated level of calculation is needed for evaluating Gibbs free energies, if trustable conformational populations is desired. Then, it can be anticipated that a quite reliable value of Gibbs free energy difference would be required to calculate accurate conformational population values (having an average uncertainty of ±1%), for ΔG around 2 kcal mol^{-1} (as in the cyclooctane case). It can be seen that there is an inevitable compromise between the uncertainty *d* and ΔG, that is, smaller is the value of ΔG smaller should be *d*, in order to reach reliable predictions of conformational populations.

In the light of the comments of last paragraph we are inclined to affirm that for the cyclooctane molecule in the gas phase, the most trustable conformational population data available is the CCSD/cc-pVDZ result (or MP4(SDQ)/cc-pVDZ that differs only in 1%), that is 92% of BC and 8% of CROWN, at room temperature, with thermal corrections evaluated at the MP2 level and neglecting the low frequency torsion modes. These results are in good agreement with the experimental predictions of Dorofeeva et al. (Dorofeeva et al., 1985), which reported the population of BC to be in a range of 91–98%, at 332 K. There is indeed a contribution of ca. 8% of the CROWN form in the conformational mixture at 298 K. If the temperature is raised to 59°C (332 K), as in the experiment of Dorofeeva et al. (Dorofeeva et al., 1985), the percentage of the CROWN structure would increase to ca. 10% (CCSD/cc-pVDZ//MP2/cc-pVDZ value) and might well be detectable in the electron diffraction gas phase experiment. Therefore, the lower limit for the percentage of BC (91%) that was reported by Dorofeeva et al. (Dorofeeva et al., 1985) is definitively their best value, not the upper limit of 98%.

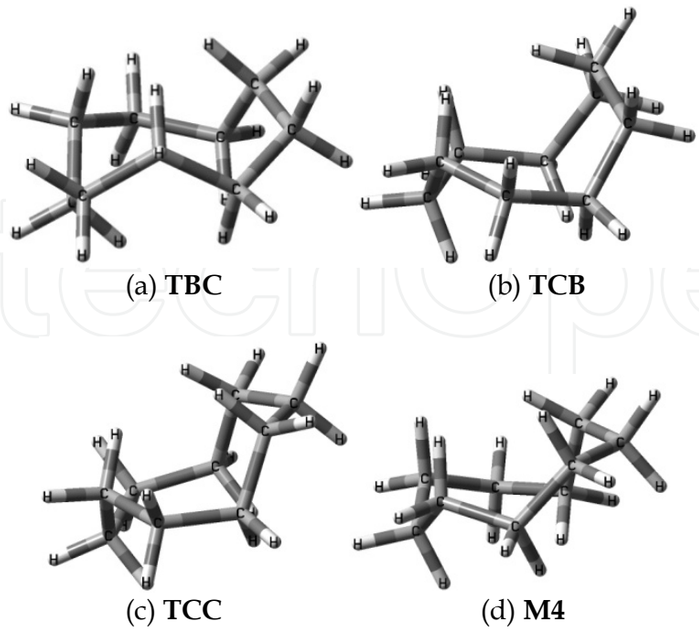
Lastly, **w**e aim to call the attention of people working on conformational analysis studies to the important problem of adding thermal corrections to the calculated relative energy values and also to the role played by the low frequency modes for the calculation of the thermal

energy corrections. We are not affirming here that the behavior observed for the cyclooctane molecule would be necessarily the same for other molecular systems. However, we should be alert to the fact that the use of the harmonic oscillator partition function to treat low frequency vibrational modes, that may be internal rotation modes, can lead to wrong predictions, and the simple approach that we used for cyclooctane may be a way out to obtain more trustable relative Gibbs free energy values. By using a high correlated *ab initio* level of theory with a reasonable basis set for calculating the electronic contribution to the total Gibbs free energy we eliminated the possibility of cancellation of errors in the *ab initio* electronic structure calculation. As we performed a systematic investigation our nice agreement with experiment cannot be viewed as just a lucky circumstance. Unfortunately there are not many accurate experimental gas phase conformational relative energy data available in the literature for comparison and we have to rely on theoretical highly correlated *ab* initio data.

4.3 Cyclononane

The literature with the focus on the conformational analysis of cyclononane is also substantial (Hendrickson, 1961; Hendrickson, 1967b; Anet & Krane, 1980; Kolossvary & Guida, 1993; Weinberg & Wolfe, 1994; Wiberg, 2003). Anet and Krane (Anet & Krane, 1980) carefully analyzed the conformational distribution of cyclononane as a function of the temperature using dynamic NMR spectroscopy and found two major forms in the equilibrium mixture (named TBC and TCB) with a third conformer (TCC) present on a small amount at higher temperature. More recently Wiberg (Wiberg, 2003) used quantum-mechanical methods to obtain structure and energy for this molecule with the MP2 prediction found in qualitative agreement with the experimental proposal (Anet & Krane, 1980). In our recent paper (Franco et al., 2007), eight distinct minimum energy conformers were located on the gas phase MP2/6-31G(d,p) PES, with the main structures shown in Figure 10. The first two isomers (TBC and TCB) were proposed in the pioneer works of Hendrickson (Hendrickson, 1961; Hendrickson, 1967a, 1967b), and Anet and Krane (Anet & Krane, 1980) described later the so called TCC (and also C1) structure. The conformation M4 (and also M6 and M7) has been found by Wiberg (Wiberg, 2003) in a theoretical *ab initio* analysis. The structure M8 was proposed by our group and represents a higher energy minimum point on the PES at the MP2 level. Experimentally, the conformational analysis was done by dynamic ^{13}C NMR at a broad range of temperature from -173 to -70°C (Anet & Krane, 1980). The measurements were carried out in solution of a solvent mixture of $CHFCl_2$ and vinyl chloride (1:2) using TMS (tetramethylsylane) as internal reference. The distribution of conformers in the equilibrium was obtained by fitting to a theoretical model, depending on chemical shift, conformational population and interconversion rate constant, to the experimental line shape.

The calculated relative energies ($\Delta E_{ele-nuc}$) are given in Table 10 where the TBC form was taken as reference. It can be seen from Table 10 that the HF and B3LYP relative energies are virtually the same, what has also been observed by Wiberg (Wiberg, 2003). At these levels of theory the TCB isomer was found to be the global minimum with the TBC only 0.1 kcal mol^{-1} higher in energy. The MPn methods predict the TBC form as the most stable in gas phase with the MP4 values found to be very close to the MP2 one. The DFT relative energies exhibit a sizeable disagreement with the MPn values, with the B3LYP and BLYP functionals exhibiting the poorest accordance with the MP2 and MP4 energies. The B3P86/6-31G(d,p) and PBE1PBE/6-31G(d,p) values show the smallest deviation, however being still far away from the *post*-HF description of the relative energy values.



(a) **TBC** (b) **TCB**

(c) **TCC** (d) **M4**

Fig. 10. MP2/6-31G(d,p) fully optimized geometries for the main conformers of cyclononane (TBC, TCB, TCC and M4).

The thermodynamic properties for the four main minimum conformers, TBC, TCB, TCC and M4, are reported in Table 11 as calculated at distinct temperatures for what experimental data are available (Anet & Krane, 1980). All thermal corrections (ΔG_T) calculations were done using the MP2/6-31G(d,p) structural parameters and harmonic frequencies, for the calculation of the enthalpic and entropic terms, including all 3N-6 normal modes in the evaluation of the vibrational partition function.

	TBC	TCB	TCC	M4	C1	M6	M7	M8
HF/6-31G(d,p)	0.0	-0.10	1.17	-	3.3	-	10.2	-
B3LYP/6-31G(d,p)	0.0	-0.08	1.34	-	3.29	-	10.3	-
BLYP/6-31G(d,p)	0.0	-0.39	1.10					
BP86/6-31G(d,p)	0.0	0.19	1.62					
B3P86/6-31G(d,p)	0.0	0.43	1.80					
PW91/6-31G(d,p)	0.0	0.19	1.65					
PBE1PBE/6-31G(d,p)	0.0	0.48	1.80					
MP2/6-31G(d,p)	0.0	1.16	2.49	3.88	3.92	7.16	11.3	10.2
MP4(SDQ)/6-31G(d,p)// MP2/6-31G(d.p)	0.0	0.84	2.07	3.55	3.72	6.87	11.01	9.92
MP4(SDTQ)/6-31G(d,p)// MP2/6-31G(d,p)	0.0	1.00	2.28	3.68	3.75	6.88	10.99	9.94

[a]From (Anet & Krane, 1980).

Table 10. Relative energies (in kcal mol^{-1}) calculated for the distinct minimum conformers of cyclononane.

	T=100.15K	T=128.15K	T=178.15K	T=298.15K
TBC	0.0[0.0]	0.0[0.0]	0.0	0.0
	94.1%[95%]	87.6%[88%]	74.9%	52.1%[40%]
TCB	0.5497[0.6]	0.4997[0.5]	0.3975	0.1217
	5.9%[5%]	12.3%[12%]	24.4%	42.4%[50%]
TCC	1.7699	1.7307	1.6440[1.6]	1.3946
	0.0%	0.1%	0.7%[1%]	5.0%[10%]
M4	3.1949	3.1507	3.0555	2.7869
	0.0%	0.0%	0.0%	0.5%

Table 11. Relative Gibbs free energy (ΔG), obtained using all 3N-6 normal modes for the evaluation of the vibrational partition function, for the four main conformations of cyclononane molecule calculated at MP4(SDTQ)/6-31G(d,p)//MP2/6-31G(d,p) level (values in kcal mol^{-1}). The Gibbs population is also given with the experimental data in brackets.

At 100.15 K the experimental data were assigned to the TBC major form and a small amount of a second conformer. The analysis was rationalized by postulating a simple conformational mixture with the TBC→TCB equilibrium being established and strongly shifted to the TBC isomer (95%) (Anet & Krane, 1980). Our MP4 results are in excellent agreement with this proposal with the Gibbs population calculated to be 94.1% (TBC) and 5.9% (TCB). Rising the temperature to 128.15 K the experimental analysis showed the population distribution equal to 88% for the major conformation (TBC) and 12% for the minor form (TCB). The theoretical results gave 87.6, 12.4 and 0.1% for TBC, TCB and TCC, respectively supporting the experimental findings. At 178.15 K the TCC form was observed at small amount, 1.0±0.5% (Anet & Krane, 1980). The theoretical determination gives 0.7% for TCC with the TBC→TCB equilibrium being slightly shifted toward the TCB species, which is present in the medium on a relative population of 24.4%. At room temperature a rough experimental estimation of the conformational population was made with the aid of MM structural and energy data, i.e., 40% of TBC, 50% of TCB and 10% of TCC. The theoretical results obtained at MP4(SDTQ)/6-31G(d,p)//MP2/6-31G(d,p) showed the following values: 52.1% of TBC, 42.4% of TCB, 5% of TCC and 0.5% of M4, in nice agreement with the experimental estimation, but with the TBC structure still found to be the global minimum. These comparisons are better summarized in Figure 11, which shows the Gibbs conformational population for the four relevant conformers of cyclononane as a function of the temperature, along with the available experimental data. The apparent disagreement between our theoretical and experimental populations at room temperature regarding to the TBC→TCB equilibrium position is certainly due to the fact that the experimental population at this temperature was not directly based on the NMR data, but a rough extrapolation (Anet & Krane, 1980). By looking at Figure 11a, where the MP4(SDTQ)/6-31G(d,p)//MP2/6-31G(d,p) Gibbs conformational population for the four relevant conformers of cyclononane is represented as a function of the temperature considering all 3N-6 harmonic frequencies, we can clearly see that in the region where the NMR spectrum was recorded (100-180K), the theoretical and experimental predictions are in excellent agreement. In Figure 11b the common sense of increasing the population of conformers having higher energy as the temperature raise is observed, with the equilibrium being shifted to TCB just above room temperature.

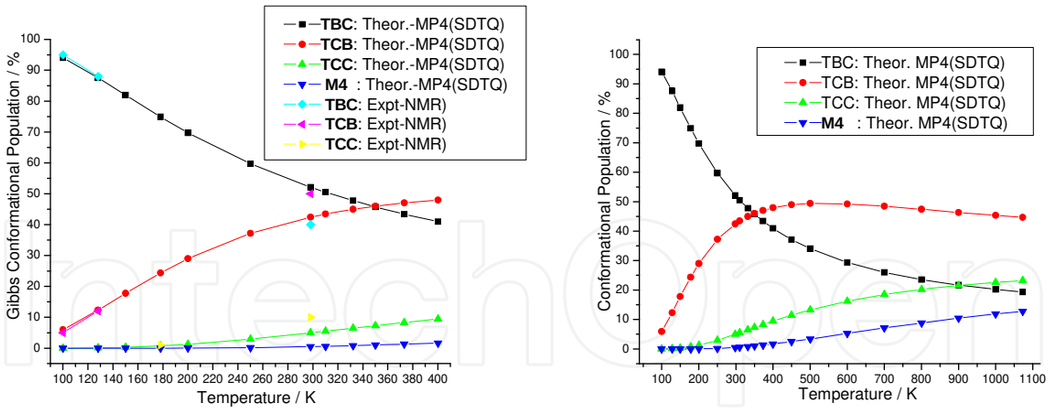


Fig. 11. MP4(SDTQ)/6-31G(d,p)//MP2/6-31G(d,p) Gibbs population for the four most relevant conformers of cyclononane as a function of the temperature. (a) All 3N-6 normal modes included in the evaluation of the vibrational partition function (available experimental data are also shown). (b) Calculated values, using the 3N-6 normal modes, on the range of 100-1073K are included.

The effect of the low frequency modes on the calculation of conformational population values is shown in Figure 12, where MP4(SDTQ)/6-31G(d,p)//MP2/6-31G(d,p) conformational population data evaluated at various temperatures are reported. In Figure 12 experimental values and theoretical results calculated including all 3N-6 normal modes and also excluding the low frequency modes from the evaluation of the vibrational partition function (HO approach) are given. It can be promptly seen the best agreement with experimental population data is obtained using all 3N-6 normal modes for the determination of the thermal correction, quite different from the behavior found for cycloheptane and cyclooctane discussed in the previous Sections.

To illustrate the dependence of thermodynamic quantities with the temperature Figure 13 shows the vibrational internal energy and entropy contributions to the thermal energy as a function of the temperature considering all 3N-6 normal modes and excluding the low frequency modes from the evaluation of the vibrational partition function. It can be easily seen that only the low frequency modes contributions are affected by the increase in the temperature.

4.4 Cyclodecane

Cyclodecane has considerably more conformational flexibility (Hendrickson, 1964; Eliel et al., 1965; Almenningen, Bastiansen & Jensen, 1966; Rounds & Strauss, 1978; Dobler, Dunitz & Mugnoli, 1966; Burgi & Dunitz, 1968; Egmond & Romers, 1969; Srinivasan & Srikrishnan, 1971; Anet & Basus, 1973; Anet, 1974; Meiboom, Hewitt & Luz, 1977; Pakes, Rounds & Strauss, 1981; Burkert, 1982; Brecknell, Raber & Ferguson, 1985; Saunders, 1987; Lipton & Still, 1988; Chang, Guida & Still, 1989; Dorofeeva et al., 1990; Ferguson et al., 1992; Kolossvary & Guida, 1993; Weinberg & Wolfe, 1994; Wiberg, 2003) than the smaller C7–C9 cycloalkanes discussed in the previous Sections. The structures of the lower-energy conformations have been studied via electron diffraction (Hilderbrandt, Wieser & Montgomery, 1973), X-ray crystallography (Shenhav & Schaeffer, 1981) and dynamic NMR spectroscopy (Pawar et al., 1998). The boat-chair-boat (BCB) conformation for the

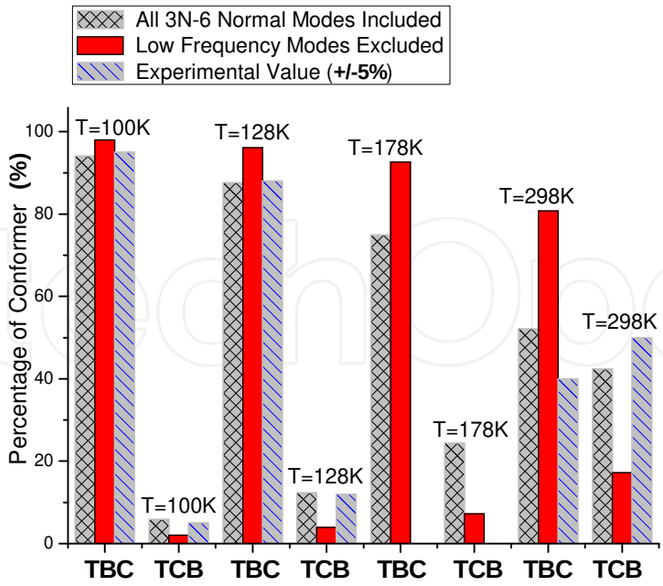


Fig. 12. MP4(SDTQ)/6-31G(d,p)//MP2/6-31G(d,p) conformational population data for cyclononane evaluated at various temperatures. Experimental values and theoretical results calculated including all 3N-6 normal modes and also excluding the low frequency modes from the evaluation of the vibrational partition function (HO approach) are shown.

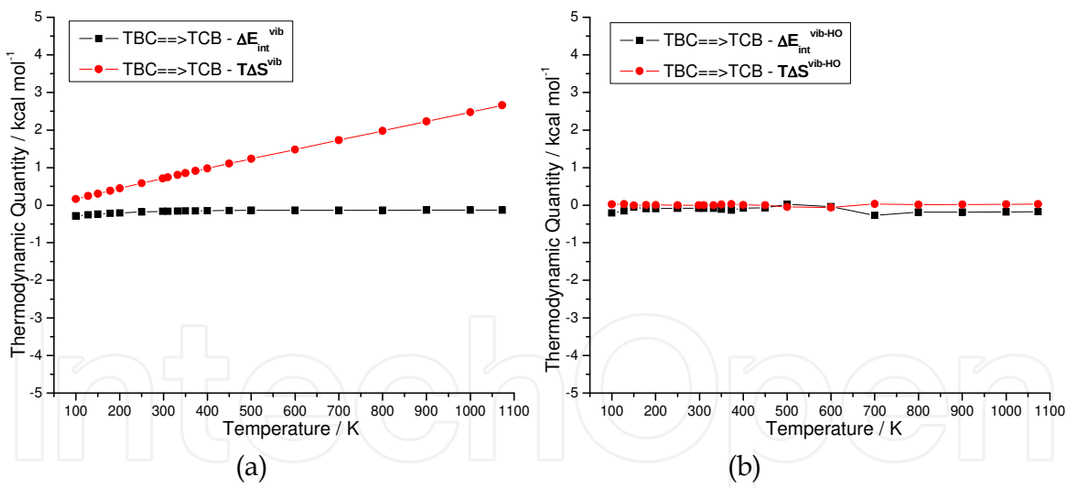


Fig. 13. MP2/6-31G(d,p) thermodynamic quantities ($\Delta E_{int,vib}$, $T\Delta S_{vib}$, in units of kcal mol^{-1}) as a function of the temperature. (a) All 3N-6 normal modes included in the evaluation of the vibration partition function. (b) Low frequency modes excluded from the calculations.

cyclodecane has been found in the solid state by X-ray diffraction (Shenhav & Schaeffer, 1981) near 173 K and assigned as the most stable form.

The low-temperature ^{13}C NMR spectra of cyclodecane showed a minor presence of a conformation assigned to the twist-boat-chair–chair (TBCC), besides the expected boat-chair-boat (BCB) conformer (Pawar et al., 1998)]. A conformational distribution having 89.6%, 5.2% and 5.2% of BCB, TBC and TBCC conformations, respectively was proposed by

Pawar and collaborators (Pawar et al., 1998) for cyclodecane based on the analysis of dynamic NMR spectroscopy carried out at 127.05 K and theoretical calculations using *ab initio* level of theory. Cyclodecane has also been studied in the gas phase at 403.15 K by means of a combination of electron diffraction and MM calculations (Hilderbrandt, Wieser & Montgomery, 1973). In this case, least square analysis of the experimental radial distribution curve, utilizing the theoretical predictions for the four lowest-energy conformations, indicated a more complex equilibrium composition: BCB, 49±3%, TBC, 35±3%, TBCC, 8±4 and BCC, 8±4%. In the present Section we discuss an accurate analysis of the thermodynamic properties and conformational populations in order to assess the influence of the low frequency vibrational modes on the calculation of thermodynamic quantities as a function of temperature for the cyclodecane molecule.

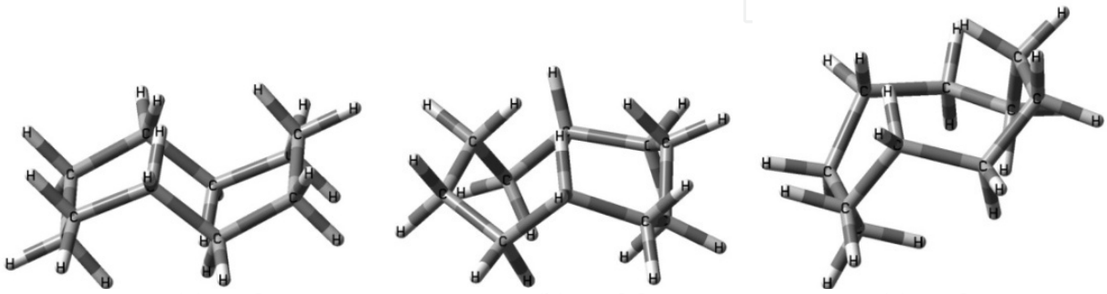
Among all possible conformers, 15 true minima were located on the PES (named S1, S2, . . . , S15), with the boat-chair-boat, BCB (S1), being the lowest energy structure, and characterized through harmonic frequency analysis. In Table 12, relative energies are shown for all conformers obtained from HF, B3LYP and MP2 levels of theory. As can be seen from Table 12, the conformations S1, S2, S3, S4 and S5, also called BCB, TBCC, TBC, BCC and TCCC, respectively, were found as the more stable forms, with relative energies within 3 kcal mol^{-1}. Based on these results, we can assume that only these five conformations are present in the equilibrium in significant amounts. The structures of the main conformers are depicted in Figure 14.

	$\Delta E_{ele-nuc}$		
	HF/6-31G(d,p)	B3LYP/6-31G(d,p)	MP2/6-31G(d,p)
S1 (BCB)	0.00	0.00	0.00
S2 (TBCC)	1.04	1.24	1.22
S3 (TBC)	0.92	0.93	1.06
S4 (BCC)	2.38	2.46	2.18
S5 (TCCC)	2.64	3.09	2.54
S6	3.15	3.23	3.54
S7	4.30	4.10	4.84
S8	4.08	3.80	4.54
S9	4.56	4.22	5.03
S10	4.64	4.43	5.65
S11	5.21	5.11	6.30
S12	6.78	6.61	6.89
S13	6.99	7.02	7.94
S14	10.94	9.01	11.23
S15	19.23	17.47	19.45

Table 12. Relative energies ($\Delta E_{ele-nuc}$ in kcal mol^{-1}) for distinct minimum energy conformers of cyclodecane

With the aim to describe the effect of electronic correlation on the relative energy, we carried out single point calculations at the MP4(SDTQ) and CCSD(T) levels, using MP2/6-31G(d,p) geometries. The results are given in Table 13, where the double slashes indicate a single point energy calculation at the geometry specified after the slash. As can be seen in Table 13, the energy variation observed at the MP2/6-31G(d,p), MP4(SDTQ)/6-31G(d,p) and

CCSD(T)/6-31G(d,p) calculations was smaller than 0.1 kcal mol^{-1}. Thus, we can conclude that the electron correlation effect accounted for at the MP2 level is satisfactory for the description of cyclodecane. A variety of DFT-based methods were also tested, including BLYP, PW91 and BP86 GGA functionals and the B3LYP, B3P86 and PBE1PBE hybrid functionals employing the 6-31G(d,p) basis set (see Table 13). Analyzing these results and having as reference the MP2/6-31G(d,p) values, it was observed that all functionals provide satisfactory relative energies, with the B3P86 and PBE1PBE functionals giving the best agreement with MP2 data. Therefore, the DFT approaches can be viewed as a feasible alternative for studying larger cycloalkanes where MP2 and higher *post*-HF calculations are computationally prohibitive.



(a) BCB (b) TBCC (c) TBC

Fig. 14. MP2/6-31G(d,p) fully optimized geometries for the main conformations of the cyclodecane molecule. (a) BCB (b) TBCC (c) TBC

	$\Delta E_{elec-nuc}$				
	BCB	TBC	TBCC	BCC	TCCC
MP2/6-31G(d,p)	0.00	1.06	1.22	2.18	2.54
MP4(SDQ)/6-31G(d,p)// MP2/6-31G(d,p)	0.00	1.00	1.14	2.20	2.48
MP4(SDQT)/6-31G(d,p)// MP2/6-31G(d,p)	0.00	1.03	1.19	2.17	2.50
CCSD/ 6-31G(d,p)// MP2/6-31G(d,p)	0.00	1.00	1.10	2.17	2.42
CCSD(T)/ 6-31G(d,p)// MP2/6-31G(d,p)	0.00	1.01	1.14	2.14	2.44
BLYP/6-31G(d,p)	0.00	0.90	1.29	2.46	3.19
B3LYP/6-31G(d,p)	0.00	0.93	1.24	2.46	3.09
BP86/6-31G(d,p)	0.00	0.96	1.25	2.41	3.07
PW91PW91/6-31G(d,p)	0.00	0.96	1.28	2.44	3.15
PBE1PBE/6-31G(d,p)	0.00	0.96	1.18	2.35	2.87

Table 13. Electronic plus nuclear relative energies ($\Delta E_{elec-nuc}$ in kcal mol^{-1}) calculated for the main conformers of cyclodecane molecule.

The effect of the quality of the basis set on the MP2 relative energies for the five main cyclodecane conformations was also investigated. In Figure 15, the relative energies for the four equilibrium processes (BCB→TBCC, BCB→TBC, BCB→BCC and BCB→TCCC) are

plotted as a function of distinct basis sets. It is noted that the relative energies are more sensitive to the basis set than to the electron correlation effect (see Table 13). The basis-set effect is more pronounced for the equilibrium involving the lower-energy conformers, for which $\Delta E_{elec-nuc}$ values are within 1 kcal mol^{-1}. The TBC isomer is more stable than TBCC at lower levels of theory (MP2/6-31G(d,p)), and the enhancement of basis set up to 6-311+G(d,p) changes the stability order, with the TBCC found as more stable. Further improvement of the basis set with inclusion of two sets of polarization functions (MP2/6-311++G(2d,2p)) predicts both forms as being almost degenerate. These calculations revealed the importance of using extended basis sets (triple-zeta) with diffuse functions, which improves significantly the description of the electronic plus nuclear-nuclear repulsion energy.

Conformational analysis for cyclodecane was performed, with the CCSD(T)/6-31G(d,p)//MP2/6-31G(d,p) results reported in Table 14 at distinct temperatures in which experimental data are available. The Gibbs populations calculated at the MP2/6-311G(d,p) level predicted the population of TBCC slightly higher than TBC, respectively 4% and 2% at T = 102.05 K. As in the previous sections the thermal correction term (ΔG_T), necessary for the calculation of thermodynamic quantities, was also partitioned into two contributions: non-harmonic (NHO) and harmonic (HO), differing by whether the low frequency modes are included or not, respectively. The total thermal correction corresponds to the sum of these two contributions. Therefore, the Gibbs free energy can be evaluated using all 3N-6 normal modes (ΔG) or ignoring the low frequency modes that corresponds to the inclusion of only the harmonic contribution (ΔG^{HO}), neglecting the ΔG_T^{NHO} term.

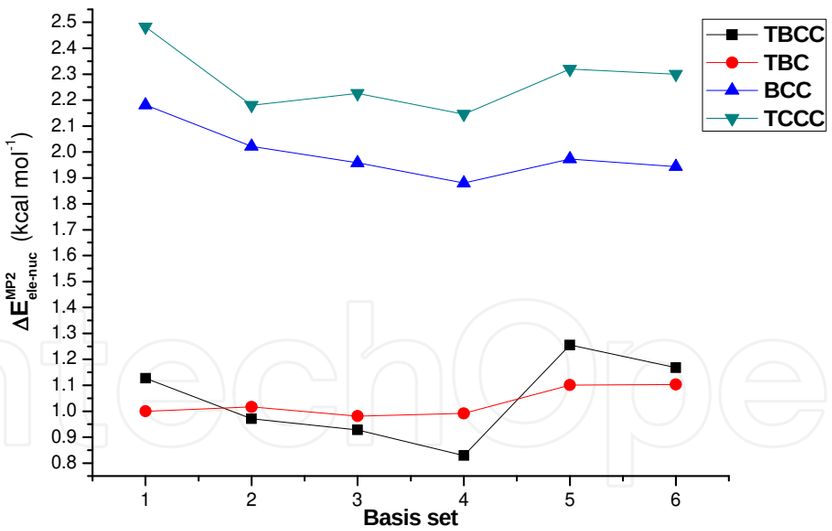


Fig. 15. Variation of the relative energy for the main conformers of cyclodecane as a function of the basis set. The BCB form was taken as reference. Basis set: 1: 6-31G(d,p); 2: 6-311G(d,p); 3: 6-31++G(d,p); 4: 6-311+G(d,p); 5: 6-311G(2d,2p); 6: 6-311++G(2d.2p).

The CCSD(T)/6-31G(d,p)//MP2/6-31G(d,p) population for the main conformers are summarized in Figure 16a, evaluated at various temperatures. Experimental values and theoretical results calculated including all 3N-6 normal modes and also excluding the low frequency modes from the evaluation of the vibrational partition function (HO approach) are

shown. It can be seen that in the case of cyclodecane the low frequency modes do not play a major role as in the case of cyclooctane, and so similar agreement with experiment is obtained excluding or not the low frequency modes from the evaluation of the vibrational partition function. As can be observed in Table 14, the thermal energy contribution due to the low frequency modes (ΔG_T^{NHO}) is small, leading to a maximum variation of ~2% in the conformational population. The variation of the conformational population as a function of the temperature is shown in Figure 16b. A similar pattern obtained previously for cyclononane is observed, however, at higher temperatures conformer BCB is the predominant.

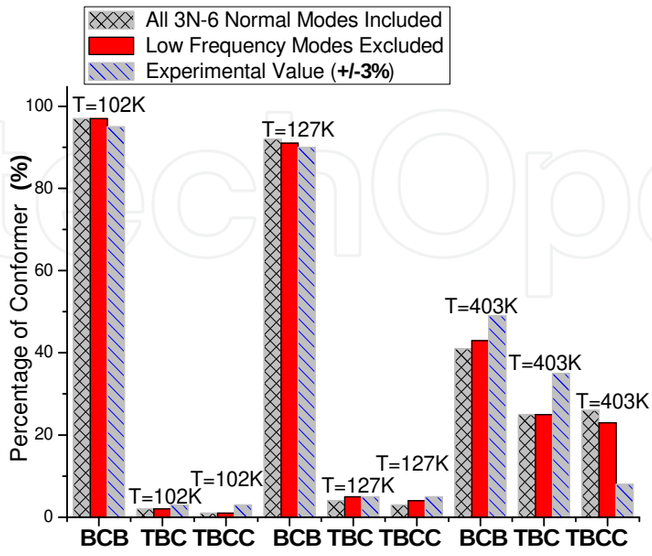
	T=102.05K			*T=127.05K*			*T=403.15K*		
	ΔG	ΔG^{HO}	pop[b]	ΔG	ΔG^{HO}	pop[b]	ΔG	ΔG^{HO}	pop[b]
BCB	0.00 (97%)	0.00 (97%)	95%	0.00 (92%)	0.00 (91%)	90%	0.00 (41%)	0.00 (43%)	49±3%
TBC	0.81 (2%)	0.80 (2%)	3%	0.78 (4%)	0.75 (5%)	5.%	0.40 (25%)	0.43 (25%)	35±3%
TBCC	0.87 (1%)	0.92 (1%)	3%	0.83 (3%)	0.79 (4%)	5%	0.36 (26%)	0.51 (23%)	8±4%
BCC	1.96 (0%)	1.96 (0%)		1.92 (0%)	1.87 (0%)		1.51 (6%)	1.54 (6%)	8±4%
TCCC	2.30 (0%)	2.38 (0%)		2.30 (0%)	2.26 (0%)		2.19 (3%)	2.24 (3%)	

[a]Gibbs population from CCSD(T)/6-31G(d,p)//MP2/6-31G(d,p) given in parenthesis. [b]Values from (Pawar et al., 1998). [c]Values from (Hilderbrandt, Wieser & Montgomery, 1973). These are rough estimates using empirical MM data (not genuinely from spectroscopic analysis).

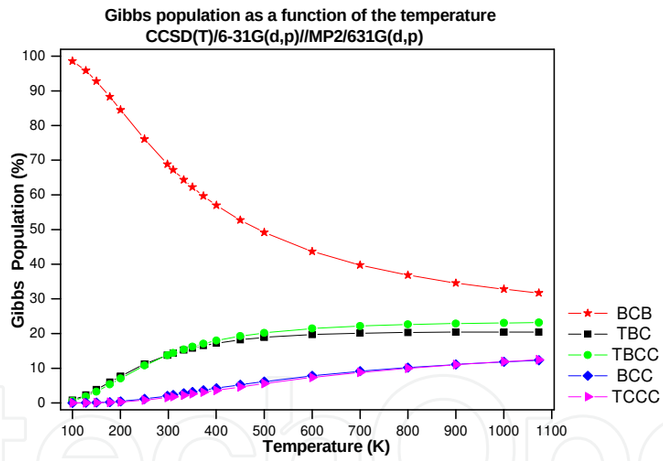
Table 14. Relative Gibbs free energy (ΔG) for the five main conformations of cyclodecane molecule calculated at CCSD(T)/6-31G(d,p)//MP2/6-31G(d,p) (values in kcal mol^{-1}) level at distinct temperatures[a].

Another important factor to be taken into account in the evaluation of the Gibbs free energy is the multiplicity (m) for each form present in the equilibrium mixture. This is the number of ways of realizing each type of conformation and can be different from unity. Thus the ΔG should be corrected for the additional term $-RTln(m_j/m_i)$, with m_j and m_i being the multiplicity for the isomers j and i respectively. According to Pawar (Pawar et al., 1998), it is necessary to assign a statistical weight of 2 to the free energies of TBCC and TBC cyclodecane conformation, since these forms may exist as two enantiomers, therefore, the factor $-RTln2$ must be included to compute the final Gibbs free energy difference. In our paper on cyclodecane (Ferreira, De Almeida & Dos Santos, 2007), the vibrational circular dichroism (VCD) spectra for the distinct forms were calculated at the B3LYP/6-31G(d,p) level. The analysis of the VCD spectra for BCB, TBC, TBCC, BCC and TCCC forms confirmed the existence of enantiomers only for TBCC, TBC and BCC structures. These results support the proposal of Pawar et al. (Pawar et al., 1998) and Kolossváry and Guida (Kolossvary & Guida, 1993), showing the existence of chiral isomers for these three forms of the cyclodecane. Therefore, the $-RTln2$ factor must be

included to compute the relative Gibbs free energy for the following equilibria BCB→TBCC, BCB→TBC and BCB→BCC.



(a)



(b)

Fig. 16. (a) CCSD(T)/6-31G(d,p)//MP2/6-31G(d,p) conformational population data for cyclodecane evaluated at various temperatures. Experimental values and theoretical results calculated including all 3N-6 normal modes and also excluding the low frequency modes from the evaluation of the vibrational partition function (HO approach) are shown. (b) Variation of population, calculated using all 3N-6 normal modes, as a function of temperature.

It is opportune to compare the conformational population values reported in Figure 16a for cyclodecane and Figure 9 for cyclooctane. A rather different behavior was observed for the cyclooctane molecule, where the exclusion of the low frequency modes (below ~650 cm^{-1}, at room temperature) has promoted a good improvement between the experimental and

theoretical data. The inclusion of all 3N-6 vibrational modes for the calculation of the vibrational partition function for cyclooctane, different from the cyclodecane case, proved to be an inadequate procedure for calculating the thermodynamic properties, leading to a total disagreement with the experimental findings. In the light of the *post*-HF *ab initio* calculations reported for cycloheptane, cyclooctane, cyclononane and cyclodecane, we can say that there is indeed an important participation of the low frequency modes for the determination of the vibrational partition function, which are used within the framework of the statistical thermodynamics formalism for the evaluation of free energies. We have so far proposed a simple and satisfactory procedure to treat these cycloalkanes; however, this approach is not meant to be a more general procedure to be applied for cycloalkanes of any size. The disagreement between the experimental and calculated conformational populations for cyclodecane was more pronounced at higher temperature (403 K). The theoretical calculation predicted the equilibrium slightly shifted toward the TBCC isomer, which is found in a ratio close to 26%. Experimentally, the TBCC population was only 8%. This disagreement may be attributed in part to the fact that at this temperature the experimental conformation distribution was not directly obtained from experiment, as in the case of low temperature measurements (Hilderbrandt, Wieser & Montgomery, 1973), but using additional information from molecular mechanics calculations. Therefore, in view of the good agreement with the experimental conformational population obtained from the low temperature NMR experiment, and also the nice agreement between *ab initio* and experimental electron diffraction population data for cycloheptane (Anconi et al., 2006) and cyclooctane (Dos Santos, Rocha & De Almeida, 2002), we believe that the CCSD(T)/6-31G(d,p)//MP2/6-31G(d,p) calculations at the temperatures range considered here can be taken as reliable within experimental uncertainties.

4.5 Large cycloalkanes

In previous Sections we reported conformational analysis of cycloheptane, cyclooctane, cyclononane and cyclodecane, where experimental population data are available, using quantum chemical methods and statistical thermodynamic formalism for the determination of conformational populations, with the main focus on conformational distribution and its dependence on the level of theory and the effect of low-frequency vibrational modes for the evaluation of entropy contribution. In these studies it was shown that for some derivatives (cycloheptane and cyclooctane), low frequency vibrations may not be considered as harmonic oscillators, having a great effect on the partition function, which leads to a significant deviation in the calculated thermodynamic properties with respect to experimental data

Our best level of calculation for relative Gibbs free energy, used as reference value, is obtained with the Eq. (22) below, where the double slash means that single point CCSD(T) energy calculations were performed using MP2 fully optimized geometries. We have also found that the use of the MP4(SDTQ) correlated level of theory leads to conformational population results very similar to CCSD(T), which consumes much more computer time, and so it can safely replace the CCSD(T) energy calculations.

$$\Delta G = \Delta E_{ele-nuc}^{CCSD(T)//MP2} + \Delta G_T^{MP2} \tag{22}$$

We can also apply Eq. (22) using the same level of calculation for the first and second terms, or other combination of levels, what may even result in a fortuitous agreement with experiment but not based on fundamental justification, only by a cancellation of errors.

Certainly, it would be ideal to use the MP4(SDTQ) or CCSD(T) level for the evaluation of relative energy and thermal correction that is undoubtedly theoretical sound, however, this is computationally prohibitive.

Aiming a better understanding of the deviation from a harmonic oscillator behavior we extended this investigation to larger cycloalkanes: cycloundecane, cyclododecane and cyclotridecane (unpublished results). According to the analysis of experimental low temperature NMR data obtained at 90.1 K (Brown, Pawar & Noe, 2003) cycloundecane exist as a mixture of two main conformers, named here 11a and 11b, being 59% of 11a and 41% of 11b. Cyclododecane has also been investigated by gas phase electron diffraction experiment at 120 ^{0}C (Atavin et al., 1989) and X-ray diffraction for a solid sample (Pickett & Strauss, 1971), both predicting the predominance of a single conformer, named 12a. The largest cycloalkane that we have been investigating is the cyclotridecane. A conformation study of a saturated 13-membered ring macrocycle, which lies on the borderline between medium and large ring systems and are generally considered very complex with a variety of conformational possibilities, has been reported by Rubin and collaborators (Rubin et al., 1984). Cyclotridecane that is placed in this borderline has defied ^{13}C NMR analysis (Dunitz & Shearer, 1960) because fast pseudorotation processes lead to a single peak, even at -135 ^{0}C, and so experimental conformational population data are not yet available. In Rubin at al. paper (Rubin et al., 1984) X-ray elucidation of the structure of a 13-atom heteromacrocycle combined with force field calculations carried out on cyclotridecane and 1,1-dimethylcyclotridecane pointed out to the existence of a main conformer denominated [33331] and a contribution of approx. 20% of minor conformers. We named this main conformer 13a. Following the structural data published by Rubin et al. (Rubin et al., 1984), just over two years ago, Valente et al. (Valente et al., 2008) reported the synthesis and X-ray structure of cyclotridecanone 2,4-dinitrophenylhydrazone, $C_{19}H_{28}N_4O_4$, a 13-membered carbocycle that was predicted to exists in the triangular [337] conformation (Valente et al., 2008). The reported molecular structure, in combination with additional evidence, indicates that [337] should be the preferred conformation of cyclotridecane and other simple 13-membered rings. We named this structure 13b. We have used the ring dihedral angles for structure 13b reported by Valente et al. (Valente et al., 2008) as an input for DFT full geometry optimization, without any geometrical constraint, and found that this is indeed a true minimum energy structure (having no imaginary frequencies) on the PES for cyclotridecane. We found that an agreement with conformational population data reported for cycloundecane and cyclododecane is obtained when all 3N-6 normal modes are used in the evaluation of the vibrational partition function (unpublished results), similar to the results reported in previous sections for cyclononane and cyclodecane. For cyclotridecane the analysis of the theoretical results are not yet conclusive, regarding the use of the HO approach. Therefore, in the light of these results it seems that for larger cycloalkanes the usual procedure of considering all 3N-6 normal modes in the calculation of relative Gibbs free energy values, implemented in most of the quantum chemical computer packages, would probably lead to satisfactory agreement with experimental population data. This is likely to hold for other macrocycles and supramolecular systems.

5. Concluding remarks

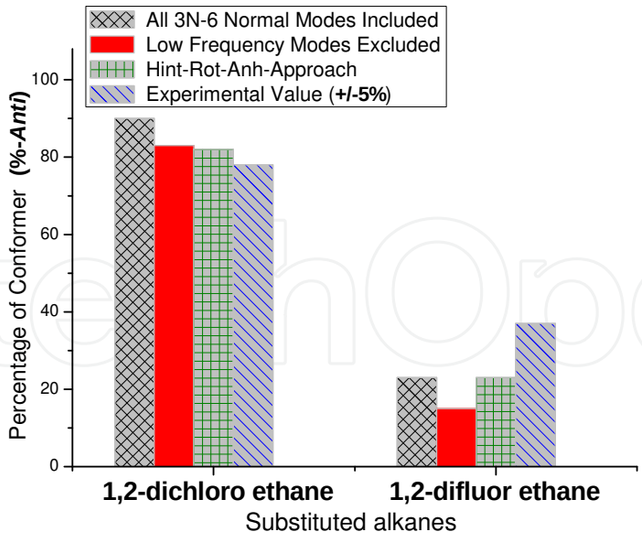
In this Chapter the theoretical formalism behind de calculation of temperature-dependent conformational population, an important subject in the area of physical organic chemistry, is

briefly reviewed, with the emphasis placed on the role played by vibrational partition function evaluated with the aid of standard statistical thermodynamics formulae. We identified which contributions to the Gibbs free energy differences (ΔG) between conformers of a given molecule are likely to be more sensitive to the level of *ab initio* theory employed for its evaluation and also the level of calculation required for an adequate description of the thermodynamic properties. The results reported here strength the validity of the procedure outlined previously to evaluate the distinct contributions to ΔG, $\Delta E_{ele-nuc}$ and ΔG_T, employing different computational procedures. The size of the molecules treated in this chapter enable the calculation of the first contribution at the MP4(SDTQ)//MP2 and CCSD(T)//MP2 single point levels and the thermal correction (ΔG_T) at the MP2 fully optimized geometry level of theory. For larger molecular systems we may use a more approximate procedure, as for exemple DFT or even DFT//PM3 level of calculation which was recently shown to produce very satisfactory results for the calculation of the Gibbs free energy of hydration of α-cyclodextrin (Nascimento et al., 2004). The less sensitivity of the thermal energy correction to the quantum chemical method employed, compared to the electronic plus nuclear-nuclear repulsion energy counterpart, is the basic reason for the suitability of this computational procedure which enables us to study large molecular systems of biological and technological interest.

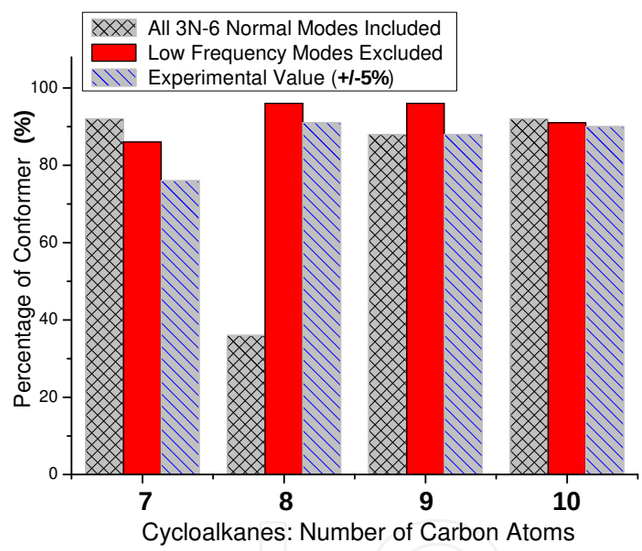
Results for two classes of molecules, for which experimental conformational population data are available, were presented: substituted alkanes and cycloalkanes. In the case of substituted alkanes we found that a treatment of low frequency vibrational as hindered rotor and anharmonicity correction leads to a fine agreement between experimental gas phase population data for 1,2-dichloro ethane and theoretical predictions, as also found for the ethane molecule. However, for 1,2-difluor ethane such procedure did not work at all, and an alternative description of the vibrational partition function must be found. The main results for the substituted alkanes discussed in this Chapter are shown in Figure 17a. For cycloalkanes a similar decomposition of the vibrational partition function was made (see equation (8b)). The very simple procedure of considering the contribution due to the low frequency modes (Q_{vib}^{NHO}) set to unity, named HO approach, was used, which is equivalent to exclude these normal modes from the evaluation of the thermal energy (ΔG_T). Such procedure worked very well for cycloheptane and cyclooctane. However, for cyclononane and cyclodecane a good agreement with experimental conformational population data is achieved considering all 3N-6 normal modes, including the low frequency modes, as harmonic oscillators, a procedure commonly used in the computational chemistry community and readily implemented in any quantum chemical computer package. Very recently we have shown that this standard procedure also worked for larger cycloalkanes containing eleven and twelve carbon atoms (unpublished results). Figure 17b show a summary of theoretical and experimental conformational population results for the cycloalkanes addressed here.

Figure 17 gives a very clear account and a quite transparent view of the importance of a separate treatment of the low frequency modes for the evaluation of the vibrational partition function, within the statistical thermodynamics formalism, according to Eq. (8b) ($Q_{vib} = Q_{vib}^{NHO}.Q_{vib}^{HO}$) which leads to the calculation of the thermal correction following Eq. (15) ($\Delta G_{T,vib} = \Delta G_{T,vib}^{NHO} + \Delta G_{T,vib}^{HO}$).

When the low frequency modes are excluded from the calculation of thermal correction it means the $Q_{vib}^{NHO} = 1$, and so, $\Delta G_{T,vib}^{NHO} = 0$, otherwise the last term is evaluated using the



(a)



(b)

Fig. 17. A summary of conformational population values (percentage of the predominant conformer A for a generic interconversion process: A→B) obtained from Gibbs free energy results (ΔG) calculated at the MP4(SDTQ)//MP2 or CCSD(T)//MP2 level of theory. The 3N-6 superscript means that all normal modes were included in the calculations, and the HO label indicate that the low frequency modes were ignored for calculation of the thermal correction (HO Approach). The *Hint-Rot-Anh* superscript means that the internal rotation (a treatment of low frequency modes as hindered rotor) and anharmonicity correction was included. (a) Susbtituted alkanes, 1,2-dichloro ethane and 1,2-difluor ethane. (b) Cycloheptane (TC→C); Cyclooctane (BC→CROWN); Cyclononane (TBC→TCB); Cyclodecane (BCB→TBC).

harmonic approximation. It can be seen from Figure 17 that the behavior for small cycloalkanes, as also substituted alkanes, is distinct from cycloalkanes containing more than eight atoms of carbon. This shows that, in the series of cycloalkanes investigated, there is no

overall agreement with experiment when the low frequency modes are excluded or not from the evaluation of the vibrational partition function. It seems that each case must be considered individually, since it may really not be possible to find a "general" vibrational partition function that precisely mimic the behavior of all cycloalkanes represented in Figure 17b, and very likely many other macrocycles and supramolecular structures. The results reported by our group on the series of cycloalkanes provide an indication that the usual procedure of considering all 3N-6 normal modes in the vibrational partition function appears to work very satisfactorily for larger macrocycles and also supramolecular systems.

6. Acknowlegment

The authors would like to thank the Brazilian agencies CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico) and FAPEMIG (Fundação de Amparo à Pesquisa do Estado de Minas Gerais) for financial support. This work is a collaboration research project of members of the Rede Mineira de Química (RQ-MG) supported by FAPEMIG. Many people have contributed to the work described in this Chapter. We particularly would like to thank Prof. Willian Rocha (UFMG), Prof. Cleber Anconi (UFLA), Prof. Mauro Franco (UFVJM) and Prof. Dalva Ferreira (UFVJM). We also thank Dr. Diego Paschoal (UFJF) for his

helpful assistance on the reference checking. Finally, the authors are greatly indebted to their families for their constant support and understanding.

7. List of symbols and abbreviations

Anh	Anharmonicity correction
B3LYP	Becke three-parameter, Lee-Yang-Parr exchange-correlation functional
B3P86	Becke three-parameter, Perdew 86 exchange-correlation functional
BLYP	Becke, Lee-Yang-Parr exchange-correlation functional
BP86	Becke, Perdew 86 exchange-correlation functional
CC	Coulpled-Cluster method
CCSD(T)	Coulpled-Cluster method with single-double and perturbative triple excitation
DFT	Density Functional Theory
ED	Electron Diffraction
$E_{ele\text{-}nuc}$	Electronic plus nuclear-nuclear repulsion energy
E_{int}	Internal energy
G	Gibbs free energy
G_T	Thermal correction to the Gibbs free energy
H	Enthalpy
HF	Hartree-Fock method
Hind-Rot	Hindered-Rotor approach
HO	Harmonic Oscillator approximation
H_T	Thermal correction for enthalpy
IR	Infrared

MM	Molecular Mechanics
MP2	Mϕller-Plesset second-order perturbation theory
MP4(SDTQ)	Mϕller-Plesset forth-order perturbation theory with single, double, triple and quadruple excitation
ν	Vibrational frequency (or wavenumber in cm^{-1})
NHO	Non-Harmonic Oscillator approach
Nlow	Number of low frequency vibrational modes
NMR	Nuclear Magnetic Resonance
PBE1PBE	Hybrid Perdew, Burke and Ernzerhof exchange-correlation functional
PES	Potential Energy Surface
PW91	Perdew and Wang's 1991 gradient-corrected correlation functional
Q	Partition function
RR	Rigid-Rotor approach
S	Entropy
TMS	Tetramethylsylane
TS	Transition State
VCD	Vibrational Circular Dichroism
V_{NN}	Nuclear-Nuclear repulsion energy
ZPE	Zero-Point Energy

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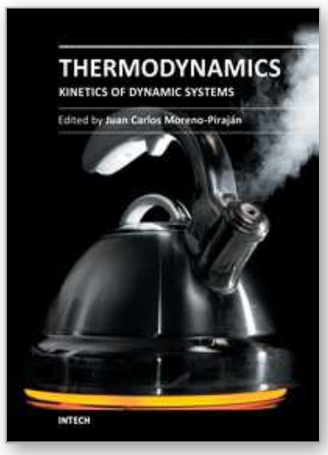
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Thermodynamics - Kinetics of Dynamic Systems
Edited by Dr. Juan Carlos Moreno PirajÃ¡n

ISBN 978-953-307-627-0
Hard cover, 402 pages
Publisher InTech
Published online 22, September, 2011
Published in print edition September, 2011

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