Coordinate Systems and the Calculation of Molecular Properties

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A number of molecular modeling techniques determine molecular properties by identifying the major low-energy conformations of a molecule or complex and evaluating the configuration integral for each such conformation. The mode integration (MINTA) technique uses normal-mode analysis in the rigid rotor approximation to facilitate evaluation of these configuration integrals in all internal degrees of freedom. This paper analyses the theory underlying MINTA and shows that the method omits numerically important terms related to the Jacobian matrix for the transformation from Cartesian to translation−rotation−vibration coordinates. It is shown that the method can be corrected either by including the missing terms or by changing to a more convenient coordinate system that does not require use of the rigid rotor approximation and hence is potentially more accurate.

Introduction

Molecular properties can be computed via sums over the most stable conformations of the system.[1−10] "Predominant states" methods, which use this approach, involve two tasks: identification of the most important low-energy conformations and evaluation of the configuration integral $\int e^{-\beta E(\mathbf{r})}\, d\mathbf{r}$ for each conformation. Interest in predominant states methods has increased recently, at least in part because of the availability of solvation models that allow solvent degrees of freedom to be treated implicitly and that thereby reduce the dimensionality of the configuration integrals to be evaluated. However, even when the solvent is treated implicitly, the evaluation of the configuration integral in an energy well can be challenging. One approach is to use the harmonic approximation, but this can produce errors if the energy well deviates much from quadratic. "Mining minima" evaluates the configurational integral in each energy well via numerical quadrature,[7] approximating bond lengths and angles as fixed. More recently, a very interesting method that aims to compute the molecular configuration integral in all degrees of freedom has been introduced. This method, "mode integration" (MINTA),[8,9] uses harmonic-biased sampling to speed the numerical evaluation of configuration integral.

We implemented MINTA but found that it did not agree with analytic configuration integrals for simple model systems. The trouble proved to lie in a subtlety of the rigid-rotor coordinate system used in MINTA. The present note describes two ways to solve this problem, one within the rigid-rotor approximation and the other more general. To support this analysis and because similar issues continue to arise in the general literature, the Appendix derives expressions for the standard chemical potential of a molecule in solution in two relevant coordinate systems.

Theory and Results

In MINTA, the full configuration integral for a given energy well i is written as an integral over the $3n - 6$ vibrational normal modes of a molecule with n atoms, calculated with a nonmass-weighted second-derivative matrix (Hessian), i.e., as if all atomic masses equalled unity (see eq 5 of ref 8). The integral for energy well i will here be termed z_i^{vib}. As in other predominant states methods, the configuration integrals of the most stable energy wells (conformations) are computed and summed to yield the overall configuration integral of the molecule: $Z^{\mathrm{vib}} = \sum_i z_i^{\mathrm{vib}}$. For simplicity, we assume henceforth that only one energy minimum contributes significantly to the overall configuration integral, but generalization to multiple energy wells is straightforward.

That the MINTA method for calculating the configuration integral is incomplete can be appreciated by considering the full expression for the standard chemical potential of a molecule in the same coordinate system used by MINTA (eq 9 in the Appendix). Clearly, the chemical potential includes integrals not only over vibrational but also over the translational and rotational coordinates that MINTA omits. These external integrals do not cancel when computing quantities of interest, such as the free energy changes associated with conformational changes and binding. Thus, if a molecule can adopt two different conformations, 1 and 2, which might, for example, represent the two anomers of a carbohydrate, then MINTA gives the ratio of the probability of state 2 to state 1 as

$$p_2/p_1 = e^{-\beta(\mu_2^\circ - \mu_1^\circ)} = \frac{Z_2^{\mathrm{vib}}}{Z_1^{\mathrm{vib}}} \tag{1}$$

where μ_i° is the standard chemical potential of state i. However, the correct expression derived from eq 9 (Appendix) is

$$p_2/p_1 = \left(\frac{I_{2,a} I_{2,b} I_{2,c}}{I_{1,a} I_{1,b} I_{1,c}}\right)^{1/2} \frac{Z_2^{\mathrm{vib}}}{Z_1^{\mathrm{vib}}} \tag{2}$$

where $I_{i,a}$, $I_{i,b}$, and $I_{i,c}$ are the principal moments of inertia of conformation i, and the ratio of moments in this expression does not equal unity except in special cases. It should be emphasized that MINTA's use of a non-mass-weighted Hessian matrix does

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not eliminate this term, which is related to the Jacobian determinant for the transformation from Cartesian coordinates to translational−rotational−vibrational coordinates, as previously noted.[11,12] Rather, when the Hessian is not mass-weighted, the inertial term in eq 2 is calculated as if all atoms had unit mass. The magnitude of the resulting correction term depends on the molecule involved and the nature of its conformational change. Thus, the value is only 1.005 for the boat−chair transition of cyclohexane (0.992 with unit atomic masses) but rises to 218 (224 with unit atomic masses) when the enzyme chorismate mutase expands from its native conformation to a fully extended form. Thus, the rotational term favors the expanded form of chorismate mutase by about −3.2 kcal/mol at room temperature. This correction is large relative to the claimed accuracy of MINTA and is therefore significant.

An additional term, derived from the translational degrees of freedom, appears when eq 9 is used to write the standard binding free energy of molecules *A* and *B*:

$$e^{-\beta\Delta G^\circ} \equiv e^{-\beta(\mu_{AB}^\circ - \mu_A^\circ - \mu_B^\circ)} = \left[C^\circ\left(\frac{M_{AB}}{M_A M_B}\right)^{3/2}\right]\left[\frac{1}{8\pi^2}\left(\frac{I_{AB,a} I_{AB,b} I_{AB,c}}{I_{A,a} I_{A,b} I_{A,c}\, I_{B,a} I_{B,b} I_{B,c}}\right)^{1/2}\right] \times \left[\frac{Z_{AB}^{vib}}{Z_A^{vib}\, Z_B^{vib}}\right] \quad (3)$$

(See Appendix for symbols.) The first two terms in brackets can be interpreted, respectively, as translational and rotational contributions to the binding constant. Again, if a non-mass-weighted Hessian is used in evaluating Z_X^{vib}, as in MINTA, then the translational and rotational terms must be evaluated with all masses set to unity.

The translational and rotational terms in eq 3 can be substantial, as illustrated by the association of a synthetic adenine receptor[13,14] (receptor C in ref 15) with methyladenine. We focus on only the single lowest-energy conformation of the free and bound molecules and compute energy with the CHARMM[16] force field as implemented in Quanta.[17] With unit atomic masses, the first two bracketed terms contribute −89.6 and −90.2 kcal/mol, respectively, to the binding free energy. The third term contributes 167.5 kcal/mol, for a net binding free energy *in vacuo* of −12.3 kcal/mol. Using actual atomic masses changes the individual terms but not the final result. Including a Generalized Born model[18] of electrostatic solvation does not change the translational term at all and changes rotational term by less than 0.1 kcal/mol, though it significantly weakens binding by increasing the vibrational term, since this includes the difference in potential energy of the free and bound conformations. Note that, although the individual bracketed terms in eq 3 have units, their product is dimensionless. The binding free energy can be written equivalently as the product of dimensionless translational, rotational, and vibrational terms by allowing each term to retain its factors of $2\pi kT/h^2$, rather than canceling them as has been done on going from eq 9 to eq 3. These dimensionless terms remain numerically significant: for the synthetic adenine receptor discussed above, the translational, rotational, and vibrational terms are 6.7, 6.1, and −25.1 kcal/mol, respectively. Note that the overall binding free energy is still −12.3 kcal/mol.

Although the rotational and translational terms that MINTA neglects can be large, the published applications of MINTA[8,9] are not likely to have incurred large numerical errors, due to cancellation of errors. Thus, the conformational changes that were studied would not have markedly altered the rotational moments of inertia; only relative free energies of binding were computed, and these involved binding of pairs of enantiomers to one type of molecular host. However, most applications will not yield such a high degree of cancellation. Fortunately, it is straightforward to evaluate the missing terms when they are expected to be important, thus correcting MINTA and extending its range of applicability.

Alternatively, it is possible to compute configuration integrals in a coordinate system for which the apparently mass-dependent Jacobian terms do not appear at all. The key is the method for separating internal from external coordinates. MINTA in effect uses the Eckart−Sayvetz (ES) conditions[19−23] that external motions of the molecule not affect its internal *kinetic* energy (see Appendix). The resulting separation holds only when the vibrational motions do not change the rotational moments of inertia significantly, i.e., when the rigid-rotor approximation is a good one. The ES conditions simplify dynamical study of molecules because they yield an approximate separation between internal and external momenta. However when dynamics are not at issue, it is simpler, more accurate, and more natural to separate internal from external coordinates by applying the condition that motion along the external coordinates does not affect the *potential* energy of the molecule. (Note that a finite motion along the external rotations obtained from the ES conditions distorts the molecule and thus changes its potential energy.)

The Appendix reviews how such a coordinate system can be set up by defining six coordinates, associated with three atoms, as external coordinates, and it provides an expression for the standard chemical potential in these coordinates. These internal coordinates are termed "anchored" because six atomic coordinates are held fixed while the internal integral is evaluated. Note that no rigid-rotor approximation is now required because the potential energy is now completely independent of the external coordinates. The resulting expression for the standard chemical potential of a molecule in solution is given in the Appendix, and conformational ratios and binding free energies are given by:

$$p_2/p_1 = Z_2^{anc}/Z_1^{anc} \quad (4)$$

$$e^{-\beta\Delta G^\circ} = \frac{C^\circ}{8\pi^2}\frac{Z_{AB}^{anc}}{Z_A^{anc}\, Z_B^{anc}} \quad (5)$$

where Z^{anc} is the internal configuration integral in anchored coordinates. Given an energy model, Z^{anc} can be evaluated by computing the Hessian in only the $3n - 6$ internal coordinates and then using either the harmonic approximation or MINTA-like harmonic-biased sampling to evaluate the configuration integral. Although no mass-dependent terms appear in eqs 4 and 5, they yield results numerically equal to those in eqs 2 and 3 so long as the rigid-rotor approximation holds; when the rigid rotor approximation does not hold, then the anchored coordinates are clearly preferable. We have confirmed the agreement of the two methods with numerical tests, including simple cases for which analytic results can be obtained; a subsequent report will discuss numerical aspects of MINTA and related methods.

Conclusions

In summary, MINTA uses the rigid rotor approximation but equates the full configuration integral to the integral over only

vibrational coordinates, where the vibrational integral is evaluated by a harmonic-biased sampling algorithm. The method is incomplete because it omits numerically significant integrals over rotational and translational coordinates, but it can be completed by inclusion of these terms. Alternatively, the configuration integral can be evaluated in a coordinate system that does not require the rigid rotor approximation, resulting in a simpler and more general method that will be presented in more detail in a separate publication.

Before concluding, it is worth remarking upon the three bracketed terms in eq 3. These have been linked respectively with changes in translational, rotational, and internal free energy upon binding, and a number of papers have examined this partitioning. However, although these terms individually depend on the atomic masses, the binding affinity on the left-hand side of the equation does not depend on mass so long as classical statistical thermodynamics holds. Moreover, the equally valid eq 5 does not partition the affinity into translational, rotational, and vibrational contributions and is explicitly independent of the atomic masses. Arguably, then, the common practice of partitioning binding free energies into translational, rotational and vibrational contributions is not particularly meaningful.

Appendix

The standard chemical potential of species X can be written as[24−26]

$$\mu_{\mathrm{X}}^{\circ} = -RT \ln\left(\frac{1}{V_{N,\mathrm{X}}C^{\circ}} \frac{Q_{N,\mathrm{X}}(V_{N,\mathrm{X}})}{Q_{N,0}(V_{N,0})}\right) \tag{6}$$

Here $Q_{N,\mathrm{X}}(V_{N,\mathrm{X}})$ is the canonical partition function for a system at volume $V_{N,\mathrm{X}}$ and containing a large number, N, of solvent molecules and one solute molecule X. C° is the standard concentration—typically 1 mol/L—and $V_{N,\mathrm{X}}$ is adjusted to establish standard pressure of 1 atm. Similarly, $Q_{N,0}(V_{N,0})$ is the canonical partition function for the N solvent molecules without the solute, now at a slightly different equilibrium volume $V_{N,0}$ that also corresponds to standard pressure. (A pressure−volume term that is usually negligible for aqueous systems has been omitted.[26]) The quantity μ_{X}° can be derived by separating external (translational and rotational) from internal (conformational) coordinates. The integrals over external degrees of freedom are then carried out analytically, leaving the difficult integral over the internal degrees of freedom to be determined by numerical methods. The following subsections derive the standard chemical potential with two methods of separating internal from external coordinates: the familiar rigid rotor approximation and "anchored" coordinates. For simplicity, it is assumed that only one energy well contributes significantly to the chemical potential, but generalization to multiple energy wells is straightforward.

Rigid-Rotor Approximation. MINTA uses the rigid rotor approximation to separate internal from external coordinates. In the rigid rotor approximation, the separation of the external coordinates of molecule X from its internal coordinates is based upon the Eckart−Sayvetz (or Eckart) conditions.[19−23] Intuitively, the Eckart−Sayvetz conditions are that displacements along mass-weighted internal coordinates contribute to neither the translational nor the angular momenta of the molecule. These conditions approach exactness only for infinitesimal vibrations. The external coordinates are associated with the motion of the center of mass and with rotations about the principle moments of inertia. The internal coordinates are associated with $3n - 6$ vibrational modes.[23]

The Hamiltonian of one molecule of X in solution with N molecules of solvent—needed for $Q_{N,\mathrm{X}}$ in eq 6—may be written as[23]

$$H_{N,\mathrm{X}} \approx \frac{P_x^2 + P_y^2 + P_z^2}{2M_{\mathrm{X}}} + \frac{P_a^2}{2I_{\mathrm{X},a}} + \frac{P_b^2}{2I_{\mathrm{X},b}} + \frac{P_c^2}{2I_{\mathrm{X},c}} + \frac{1}{2}\sum_{i=1}^{3n_{\mathrm{X}}-6} P_i^2 + \sum_{j=1}^{Nn_{\mathrm{S}}} \frac{p_{x,j}^2 + p_{y,j}^2 + p_{z,j}^2}{2m_j} + U(x,y,z,\zeta_a,\zeta_b,\zeta_c,\mathbf{q},\mathbf{r_S}) \tag{7}$$

Here P_x, P_y, and P_z are the momenta of molecule X associated with motion of its center of mass along the lab-frame x, y, and z coordinates and M_{X} is its total mass; P_a, P_b, and P_c are the angular momenta of the molecule around its principal axes a, b, and c with associated moments of inertia $I_{X,a}$, $I_{X,b}$, and $I_{X,c}$; P_i is the momentum associated with the ith internal coordinate, where n_{X} is the number of atoms in molecule X; $p_{x,j}$, $p_{y,j}$, and $p_{z,j}$ are the lab-frame Cartesian momenta of solvent atoms j, where n_{S} is the number of atoms per solvent molecule and m_j is the mass of atom j; and U is the potential energy as a function of the position and orientation of X $(x,y,z,\zeta_a,\zeta_b,\zeta_c)$, the internal coordinates of X $(\mathbf{q})$, and the positions of all the solvent atoms $(\mathbf{r_S})$. Masses do not appear explicitly in the internal kinetic energy term because the internal coordinates are mass-weighted.[23] Note that no assumption has been made regarding regarding the harmonicity of the potential energy. The Hamiltonian for N solvent molecules, needed for $Q_{N,0}$, is

$$H_{N,0} = \sum_{j=1}^{Nn_{\mathrm{S}}} \frac{p_{x,j}^2 + p_{y,j}^2 + p_{z,j}^2}{2m_j} + U(\mathbf{r_S}) \tag{8}$$

Equations 6−8 are now combined with the classical expression for the partition function,[27] the momentum integrals of X are evaluated, the momentum integrals of the solvent are evaluated and canceled, and a solvation term[26] W is derived, allowing the standard chemical potential of X in solution to be written as

$$\mathrm{e}^{-\beta\mu_X^{\circ}} = \left[\frac{1}{C^{\circ}}\left(\frac{2\pi M_{\mathrm{X}}kT}{h^2}\right)^{3/2}\right]\left[8\pi^2\left(\frac{2\pi kT}{h^2}\right)^{3/2}(I_{\mathrm{X},a}I_{X,b}I_{X,c})^{1/2}\right] \times \left[\left(\frac{2\pi kT}{h^2}\right)^{\frac{3n_{\mathrm{X}}-6}{2}} Z_{\mathrm{X}}^{\mathrm{vib}}\right] \tag{9}$$

where

$$Z_{\mathrm{X}}^{\mathrm{vib}} \equiv \int \mathrm{e}^{-\beta(U(\mathbf{q})+W(\mathbf{q}))}\,\mathrm{d}\mathbf{q}$$

$$W(\mathbf{q}) \equiv -RT \ln\left(\frac{\int \mathrm{d}\mathbf{r}_S\, \mathrm{e}^{-\beta\Delta U(\mathbf{q},\mathbf{r_S})}\mathrm{e}^{-\beta U(\mathbf{r_S})}}{\int \mathrm{d}\mathbf{r}_S\, \mathrm{e}^{-\beta U(\mathbf{r_S})}}\right)$$

$$\Delta U(\mathbf{q},\mathbf{r_S}) \equiv U(\mathbf{q},\mathbf{r_S}) - U(\mathbf{q}) - U(\mathbf{r_S}) \tag{10}$$

Here $Z_{\mathrm{X}}^{\mathrm{vib}}$ is the molecular configuration integral over the mass-weighted internal coordinates appropriate to the rigid rotor approximation; $U(\mathbf{q})$ and $W(\mathbf{q})$ are, respectively, the gas-phase potential energy and the solvation energy of X as a function of conformation; and h is Planck's constant. Each bracketed quantity is dimensionless.

Anchored Coordinates. The rigid rotor approximation applies only in the limit where the vibrational motions are infinitesimal. For classical statistical thermodynamics, this approximation can be eliminated by using a different separation between internal and external coordinates. To begin, lab-frame

Cartesian coordinates are used to write the Hamiltonian of a molecule of species X, along with N solvent molecules:

$$H = \sum_{i=1}^{n_X} \frac{p_{x,i}^2 + p_{y,i}^2 + p_{z,i}^2}{2m_i} + \sum_{j=1}^{Nn_S} \frac{p_{x,j}^2 + p_{y,j}^2 + p_{z,j}^2}{2m_j} + U(\mathbf{r}_X, \mathbf{r}_S) \tag{11}$$

The first sum contains the kinetic energies of the atoms of the solute; the second sum contains the kinetic energies of the N solvent atoms; and U is the potential energy, which depends on all the atomic coordinates. Combining this expression with eq 8, integrating over momenta, canceling the solvent momentum integrals, and encapsulating solvent effects in a solvation energy term[26] yield an expression for the ratio of partition functions found in eq 6:

$$\frac{Q_{N,X}}{Q_{N,0}} = \frac{1}{h^{3n_X}} \prod_{i=1}^{n_X} (2\pi kTm_i)^{3/2} \int e^{-\beta[U(\mathbf{r}_X) + W(\mathbf{r}_X)]} d\mathbf{r}_X \tag{12}$$

We now define external coordinates that do not affect the conformation and hence the potential energy of the molecule.[28] This is accomplished by setting up a molecular frame of reference that moves and rotates with the molecule and expressing the internal coordinates of the molecule with respect to this frame. An atom, indexed as 1, is chosen as the origin of coordinates of the molecular frame. The conformational energy of the molecule does not depend on the three lab-frame Cartesian coordinates of this origin, so the integral over this position can be factored out and evaluated as the volume of the container ($V_{N,X}$). The z axis of the molecular frame is then defined as the unit vector directed from atom 1 toward an atom 2 that is bonded to atom 1. The conformational energy does not depend on the 2 spherical coordinates (θ_{ext},ϕ_{ext}) that specify the lab-frame orientation of this axis, but only upon the distance of atom 2 from atom 1 (b_2). Therefore, θ_{ext},ϕ_{ext} are external coordinates, and one can immediately integrate over them to obtain a contribution of $4\pi b_2^2$ to the integral in eq 12. Given an atom 3 bonded to atom 2, the plane formed by atoms 1, 2, and 3 defines the $x-z$ plane of the molecular frame, and the molecular y axis is directed along the cross-product of axes 1−2 and 2−3. The energy of the molecule is independent of the orientation of the $x-z$ plane, so the rotation angle about the 1−2 bond (ζ_{ext}) is the sixth external coordinate. The spatial integral over this coordinate is $2\pi b_3 \sin\theta_3$, where θ_3 is the bond angle defined by atoms 1, 2, and 3. For a bimolecular complex, the internal frame of reference is defined with one molecule and then used for the entire complex.

The conformation of the molecule is now specified via $3n_X - 6$ internal Cartesian coordinates $\mathbf{r}_{int}$ in the molecular frame just defined. Combining eqs 6 and 12 yields

$$e^{-\beta\mu_X^\circ} = \left(\frac{1}{h^{3n_X}} \prod_{i=1}^{n_X} (2\pi kTm_i)^{3/2} \frac{8\pi^2}{C^\circ} Z_X^{anc} \right)$$

$$Z_X^{anc} \equiv \int b_2^2 b_3 \sin\theta_3 \, e^{-\beta[U(\mathbf{r}_{int}) + W(\mathbf{r}_{int})]} \mathbf{r}_{int} \tag{13}$$

Here Z_X^{anc} is the internal configuration integral of molecule X in the present "anchored" internal coordinates. The factor of $b_2^2 b_3 \sin\theta_3$ depends on the internal coordinates $\mathbf{r}_{int}$ and hence belongs within the integral. However, because the integrand is sharply peaked at the equilibrium values of these bond lengths and angles, the factor can to good approximation be assumed constant and removed from the integral. Also, the integral over internal Cartesian coordinates can, if so desired, be rewritten in the more familiar form of an integral over bond-lengths, bond-angles, and torsional rotations.[28−30]

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