(4) Elderfield, D. J. *J. Phys. A: Math. Gen.* **1978**, *11*, 2483; *J. Phys. C: Solid State Phys.* **1980**, *13*, 5883.
(5) des Cloizeaux, J. *J. Phys. (Orsay, Fr.)* **1981**, *42*, 635.
(6) Oono, Y.; Freed, K. F. *J. Phys. A: Math. Gen.* **1982**, *15*, 1931.
(7) Moore, M. A. *J. Phys. (Orsay, Fr.)* **1977**, *38*, 265.
(8) Moore, M. A.; Al-Noaimi, G. F. *J. Phys. (Orsay, Fr.)* **1978**, *39*, 1015.
(9) Elderfield, D. J. *J. Phys. A: Math. Gen.* **1981**, *14*, 3367.
(10) Daoud, M.; Jannink, G. *J. Phys. (Orsay, Fr.)* **1976**, *37*, 973.
(11) Schäfer, L.; Witten, T. A. *J. Phys. (Orsay, Fr.)* **1980**, *41*, 459.
(12) Duplantier, B. *J. Phys. (Orsay, Fr.)* **1982**, *43*, 991.
(13) Brézin, E.; Le Gillou, J. C.; Zinn Justin, J. In "Phase Transitions and Critical Phenomena"; Domb, C., Green, M. S., Eds.; Academic Press: New York, 1976; Vol. 6, p 125.
(14) de Gennes, P.-G. *Phys. Lett. A* **1972**, *38*, 339.
(15) Bruce, A. D.; Wallace, D. J. *J. Phys. A: Math. Gen.* **1976**, *9*, 1117.
(16) de Gennes, P.-G. "Scaling Concepts in Polymer Physics"; Cornell University Press: Ithaca, NY, 1979.
(17) Schäfer, L.; Horner, H. *Z. Phys. B* **1978**, *29*, 251.
(18) Cotton, J. P.; Nierlich, M.; Boué, F.; Daoud, M.; Farnoux, B.; Jannink, G.; Duplessix, R.; Picot, C. *J. Chem. Phys.* **1976**, *65*, 1101.
(19) des Cloizeaux, J. *J. Phys. (Orsay, Fr.)* **1975**, *36*, 281.
(20) Schäfer, L. *Macromolecules* **1982**, *15*, 652.
(21) Bervillier, C. *Phys. Rev. B* **1976**, *14*, 4964.
(22) Witten, T. A.; Schäfer, L. *J. Phys. A: Math. Gen.* **1978**, *11*, 1843.
(23) Cotton, J. P. *J. Phys. Lett. (Orsay, Fr.)* **1980**, *41*, 231.
(24) Miyaki, Y.; Fujita, H. *Macromolecules* **1981**, *14*, 742.
(25) Norisuye, T.; Kawahara, K.; Teramoto, A.; Fujita, H. *J. Chem. Phys.* **1968**, *49*, 4330.
(26) Berry, G. C. *J. Chem. Phys.* **1966**, *44*, 4550.
(27) Yamamoto, A.; Fujii, M.; Tanaka, G.; Yamakawa, H. *Polym. J.* **1971**, *2*, 799.
(28) Fukuda, M.; Fukutomi, M.; Kato, Y.; Hashimoto, T. *J. Polym. Sci., Polym. Phys. Ed.* **1974**, *12*, 871.
(29) Matsumoto, T.; Nishioka, N.; Fujita, H. *J. Polym. Sci., Part A-2* **1972**, *10*, 23.
(30) Kato, T.; Miyaso, K.; Nagasawa, M. *J. Phys. Chem.* **1968**, *72*, 2161.
(31) Miyaki, Y.; Einaga, Y.; Fujita, H. *Macromolecules* **1978**, *11*, 1180.
(32) Noda, I.; Kato, N.; Kitano, T.; Nagasawa, M. *Macromolecules* **1981**, *14*, 668.
(33) Daoud, M.; Cotton, J. P.; Farnoux, B.; Jannink, G.; Sarma, G.; Benoit, H.; Suplessix, R.; Picot, C.; de Gennes, P.-G. *Macromolecules* **1975**, *8*, 804.
(34) Cotton, J. P.; Farnoux, B.; Jannink, G. *J. Chem. Phys.* **1972**, *57*, 290.
(35) Nose, T.; Chu, B. *Macromolecules* **1979**, *12*, 590, 1122; **1980**, *13*, 122.
(36) Schick, M. J.; Doty, P.; Zimm, B. H. *J. Chem. Phys.* **1950**, *72*, 530.
(37) Strazielle, C.; Benoît, H. *Macromolecules* **1975**, *8*, 203.
(38) Okano, K.; Wada, E.; Kurita, K.; Hiramatsu, H.; Fukuro, H. *J. Phys. Lett. (Orsay, Fr.)* **1979**, *40*, 171.
(39) Richards, R. W.; Maconnachie, H.; Allen, G. *Polymer* **1978**, *19*, 266.
(40) Ohta, T.; Oono, Y. *Phys. Lett.* **1982**, *89A*, 460.
(41) Ohta, T.; Nakanishi, A., preprint.
(42) Witten, T. A.; Prentis, J. J. *J. Chem. Phys.* **1982**, *77*, 4247.
(43) Obukhov, S. P. *J. Phys. A: Math. Gen.* **1982**, *15*, L211.
(44) Domb, C.; Barrett, A. J. *Polymer* **1976**, *17*, 179.
(45) Sometimes such an approach is critized because it uses the so-called "$n = 0$ limit".[14] A little thought reveals that this criticism lacks any foundation.[43] Furthermore, all the other RG methods suggested use the same diagrammatic expansion as the "field theoretic" approach. Order for order, these approaches can be transformed into each other by applying some standard (Laplace) transformations.

Evaluation of the Configurational Entropy for Proteins: Application to Molecular Dynamics Simulations of an α-Helix

Ronald M. Levy,*[†] Martin Karplus,[‡] Joseph Kushick,[§] and David Perahia[∥]

Department of Chemistry, Rutgers, The State University of New Jersey, New Brunswick, New Jersey 08903, Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138, Department of Chemistry, Amherst College, Amherst, Massachusetts 01002, and Laboratoire d'Enzymologie Physicochimique et Moleculaire, Universite de Paris-Sud, Orsay, France.

Received July 5, 1983

ABSTRACT: In this paper we reformulate and extend a method proposed recently for estimating the classical configurational entropy difference between molecular conformations of proteins from molecular dynamics simulations. The method involves a quasi-harmonic oscillator approximation, in which a temperature-dependent (quasi-harmonic) Hamiltonian for the system is parameterized from a detailed computer simulation. The quasi-harmonic potential function is assumed to have a quadratic form with the coefficients chosen so that the mean square fluctuations of the coordinates evaluated from an ensemble average within the harmonic approximation have the same values as the results obtained from a molecular dynamics trajectory on the complete anharmonic potential surface, while the quasi-harmonic kinetic energy function is similar to the standard harmonic expression. It is shown that with the quasi-harmonic Hamiltonian, the effective vibrational frequencies and normal modes can be obtained. This makes possible a detailed comparison with the results obtained from the harmonic approximation and provides a simple procedure for estimating the quantum corrections to thermodynamic properties. The results of vibrational normal mode and molecular dynamics simulations for a polypeptide α-helix are used to calculate the harmonic and quasi-harmonic approximations to the entropy of this model system at three temperatures, 5, 100, and 300 K. The entropy difference ΔS between the two sets of calculations provides an estimate of the importance of anharmonicity in the determination of the configurational entropy.

Introduction

An understanding of the factors that determine the conformational stability and the binding of ligands to proteins requires a thermodynamic analysis. The observed thermodynamic changes in these systems are often the result of a delicate balance between large opposing effects.[1-5] For the analysis of entropy changes associated with different conformational states of proteins it has proved useful to divide the problem into the consideration of (1) hydrophobic effects associated with changes in the ordered state of water molecules and (2) intramolecular "vibrations" associated with changes in the atomic fluctuations of the protein and ligand about mean conforma-

---

[†] Rutgers, The State University of New Jersey.
[‡] Harvard University.
[§] Amherst College.
[∥] Universite de Paris-Sud.

0024-9297/84/2217-1370$01.50/0

tions. It has been suggested[6] that these two contributions to the change in entropy are of about equal importance. A method has recently been proposed for the theoretical calculation of the intramolecular contribution to the entropy change using the results of molecular dynamics simulations.[7] The method involves a quadratic approximation to the intramolecular potential energy for the system. The approximate potential energy function is determined by requiring the mean square fluctuations in the internal coordinates evaluated with the quadratic potential to have the same values as the results obtained from a protein molecular dynamics trajectory on the complete anharmonic potential surface ("quasi-harmonic approximation"). Thus some effects of anharmonicity, including the temperature dependence of the effective potential, are accounted for in the evaluation of the vibrational entropy. In the illustrative examples presented previously,[7] the results of normal model calculations (the standard harmonic approximation) were used to evaluate entropy changes for a model α-helix. Since within the quasi-harmonic approximation it is possible to partially incorporate anharmonicity in the thermodynamic quantities, it is important to compare the results of calculations of the entropy in the harmonic approximation with calculations for the same systems using the quasi-harmonic oscillator approximation. The difference ΔS between the two calculations provides an estimate of the contribution of anharmonicity to the thermodynamics of the systems investigated.

In this paper we introduce a quasi-harmonic approximation to both the potential and kinetic energy that makes it possible to define a temperature-dependent Hamiltonian which is a quadratic function of the internal coordinates and their conjugate momenta. We present the formalism for evaluating the quasi-harmonic vibrational entropy from a temperature-dependent quadratic Hamiltonian and show explicitly the relationship between the vibrational and configurational entropy for the quasi-harmonic model. We emphasize the factors involved in the transformation to internal coordinates and apply the method to the calculation of the entropy of a decaglycine α-helix at a series of temperatures. We compare the quasi-harmonic results from molecular dynamics simulations[11] with the values obtained from the harmonic oscillator approximation.

Formulation

The classical partition function for a macromolecule can be expressed as

$$Z = \frac{1}{h^{3N}} \int e^{-\beta \mathcal{H}}\, d\mathbf{p}_x\, d\mathbf{x} \qquad (1)$$

where $\mathcal{H}$ is the classical Hamiltonian for the system expressed in terms of Cartesian coordinates $\mathbf{x}$ and conjugate momenta $\mathbf{p}_x$, h is Planck's constant, and $\beta = (1/k_BT)$. The momentum integrations can be performed directly in Cartesian coordinates and the resulting configurational partition function is a function of $3N$ coordinates; for a given configuration the range of integration over the coordinates is restricted appropriately. Karplus and Kushick[7] introduced a quadratic approximation for the potential energy to evaluate the configurational entropy of an α-helix and showed how the entropy could be calculated from the temperature-dependent variances and covariances of the internal coordinates obtained from molecular dynamics trajectories, although the actual calculations were restricted to the harmonic approximation.[7] In this paper we consider the complete Hamiltonian $\mathcal{H}$ as a sum of internal plus external Hamiltonians and approximate the potential by the quadratic form used in the previous work.[7] To facilitate the comparison of the quasi-harmonic oscillator approximation with the standard vibrational normal mode analysis we make the rigid rotator assumption and neglect rotation–vibration coupling to be able to solve the normal mode problem with the quasi-harmonic Hamiltonian. While this is expected to be a good approximation, rotation–vibration coupling can be incoporated into the model, in principle. The resulting partition function can then be factored and we obtain

$$Z \approx Z_{\text{trans}} Z_{\text{rot}} Z_{\text{vib}} \qquad (2a)$$

where Z_{trans} and Z_{rot} are the translational and rotational partition functions and the vibrational partition function has the form

$$Z_{\text{vib}} = \frac{1}{h^{3N-6}} \int e^{-\beta H}\, d\mathbf{p}_q\, d\mathbf{q} \qquad (2b)$$

The internal Hamiltonian H depends on the $3N - 6$ internal displacement coordinates, q, and conjugate momenta $\mathbf{p}_q$. In both the harmonic and quasi-harmonic oscillator approximations it is assumed that H can be written as a quadratic function of the $3N - 6$ internal coordinates and conjugate momenta:[8]

$$H = \tfrac{1}{2}\mathbf{p}_q \cdot \mathbf{G} \cdot \mathbf{p}_q + \tfrac{1}{2}\mathbf{q} \cdot \mathbf{F} \cdot \mathbf{q} \qquad (3)$$

where $\mathbf{F}$ and $\mathbf{G}$ are respectively potential and kinetic energy matrices. The form for $\mathbf{F}$ depends upon whether we are considering a harmonic or a quasi-harmonic approximation. In the usual harmonic approximation $\mathbf{F}$ is given by

$$F_{ij} = \left(\frac{\partial^2 V}{\partial q_i \partial q_j} \right)_{\mathbf{q}_0} \qquad \text{(harmonic approximation)} \quad (4)$$

where $\{q_0\}$ are the energy-minimum coordinates. Thus, $\mathbf{F}$ is the matrix of force constants, whose values are the second derivatives of the potential energy evaluated at the conformational energy minimum. In the quasi-harmonic approximation, the elements of $\mathbf{F}$ are

$$F_{ij} = k_BT[\sigma^{-1}]_{ij} \qquad \text{(quasi-harmonic approximation)} \quad (5a)$$

$$\sigma_{ij} = \langle (q_i - \langle q_i \rangle)(q_j - \langle q_j \rangle) \rangle \qquad (5b)$$

where $[\sigma^{-1}]$ is the inverse of the matrix σ and σ contains the temperature-dependent variances (diagonal elements) and covariances (off-diagonal elements) of the internal coordinate fluctuations.[7] The elements of σ can be calculated directly from molecular dynamics or Monte Carlo simulations. When the results of a standard normal coordinate analysis are used to evaluate σ,[7] the quasi-harmonic approximation to the potential (eq 5a) is identical with the harmonic approximation (eq 4). Karplus and Kushick considered only a quasi-harmonic approximation to the potential; in order to fully develop the quasi-harmonic oscillator model with corresponding quasi-harmonic frequencies and normal modes an approximation to the kinetic energy is also required. The kinetic energy matrix has elements

$$G_{ij} = \sum_k \left(\frac{1}{m_k} \frac{\partial q_i}{\partial x_k} \frac{\partial q_j}{\partial x_k} \right) \qquad (6)$$

where m_k and x_k are the mass and Cartesian coordinates associated with the kth atom. In the harmonic approximation the derivatives of eq 6 are evaluated at the conformational energy minimum. A particularly simple choice for the quasi-harmonic approximation to $\mathbf{G}$ is to evaluate the derivatives of eq 6 at the conformation corresponding to the average values of the internal coordinates, although other choices are possible. With the quadratic form for the internal Hamiltonian (eq 3), the partition function is a multidimensional Gaussian:

$$Z_{\mathrm{vib}} = \frac{1}{h^{3N-6}} \int \exp\left(-\beta\left\{\frac{1}{2}\mathbf{p}_q\cdot\mathbf{G}\cdot\mathbf{p}_q + \frac{1}{2}\mathbf{q}\cdot\mathbf{F}\cdot\mathbf{q}\right\}\right) \mathrm{d}\mathbf{p}_q\, \mathrm{d}\mathbf{q} \tag{7}$$

Integrating over the momenta we obtain

$$Z_{\mathrm{vib}} = (2\pi k_{\mathrm{B}}T)^{(3N-6)/2}\frac{1}{h^{3N-6}} \int \exp\left(-\beta\left\{\frac{1}{2}\mathbf{q}\cdot\mathbf{F}\cdot\mathbf{q}\right\}\right)[\det \mathbf{G}^{-1}]^{1/2}\, \mathrm{d}\mathbf{q} \tag{8}$$

The factor $(\det \mathbf{G}^{-1})^{1/2}$ is the Jacobian for the transformation from Cartesian to internal coordinates. $\det \mathbf{G}^{-1}$ is inversely proportional to the products of the moments of inertia for the molecule. By the rigid rotator approximation together with the neglect of rotation–vibration coupling, $\det \mathbf{G}^{-1}$ can be removed from the integral in eq 8. In fact, it is a reasonable approximation to assume the Jacobian is restricted to a narrow range by the potential function in the exponential of the integrand of eq 8 so that the conformational energy minimum (harmonic approximation) or average molecular dynamics (quasi-harmonic) values can be used to evaluate $\det \mathbf{G}^{-1}$. Upon assigning such fixed values to the Jacobian, one may write the partition function for the internal Hamiltonian as

$$Z_{\mathrm{vib}} = (2\pi k_{\mathrm{B}}T)^{(3N-6)/2}(1/h)^{3N-6}[\det \mathbf{G}^{-1}]_{\mathbf{q}_0}{}^{1/2}Z_{\mathrm{c}} \tag{9a}$$

where Z_{c}, the reduced configuration integral introduced by Karplus and Kushick, has the form

$$Z_{\mathrm{c}} = \int \exp\left(-\beta\left\{\frac{1}{2}\mathbf{q}\cdot\mathbf{F}\cdot\mathbf{q}\right\}\right) \mathrm{d}\mathbf{q} = \int \exp\left(-\frac{1}{2}\mathbf{q}\cdot\sigma^{-1}\cdot\mathbf{q}\right) \mathrm{d}\mathbf{q} \tag{9b}$$

as is evident from eq 5, 8, and 9. The form of Z_{c} is such that the ensemble average of the internal coordinate fluctuations, $\langle \Delta q_i \Delta q_j \rangle$, satisfies

$$\langle \Delta q_i \Delta q_j \rangle \equiv \frac{\int (\Delta q_i \Delta q_j) \exp\left(-\frac{1}{2}\mathbf{q}\cdot\sigma^{-1}\cdot\mathbf{q}\right) \mathrm{d}\mathbf{q}}{\int \exp\left(-\frac{1}{2}\mathbf{q}\cdot\sigma^{-1}\cdot\mathbf{q}\right) \mathrm{d}\mathbf{q}} \tag{10}$$

The quasi-harmonic approximation is therefore self-consistent in the sense that the ensemble averages for the internal coordinate fluctuations obtained with the quadratic Hamiltonian and Z_{c} are equal to the values obtained with the complete Hamiltonian and the molecular dynamics trajectory. It is now a simple matter to obtain the configurational entropy. From the thermodynamic relation[7]

$$S_q{}^{\mathrm{c}} = \frac{\langle V \rangle}{T} + k_{\mathrm{B}} \ln Z_{\mathrm{c}} \tag{11}$$

the configurational entropy is given by

$$S_q{}^{\mathrm{c}} = \frac{3N-6}{2}k_{\mathrm{B}} + \frac{k_{\mathrm{B}}}{2} \ln\,[(2\pi)^{3N-6}(\det \sigma)] \tag{12}$$

Equation 12 is identical with eq 10 of Karplus and Kushick for the case where all internal coordinates are included; as they point out, it may be possible to use a reduced set in some cases to simplify the calculation.[7] The change in the configurational entropy between two conformations (labeled a and b) is then simply

$$\Delta S_q{}^{\mathrm{c}} = \frac{k_{\mathrm{B}}}{2} \ln \left[\frac{\det \sigma(\mathrm{b})}{\det \sigma(\mathrm{a})}\right] \tag{13}$$

We now use the present formulation to analyze the relation between the harmonic and the quasi-harmonic approximation in greater detail than given previously. When the results of a standard normal coordinate analysis are used to evaluate the elements of σ, the quasi-harmonic approximation is identical with the harmonic approximation. To show this we write $\mathbf{F}$ in the following form:[8]

$$\mathbf{F} = (\mathbf{L}^{-1})^{+}\Lambda(\mathbf{L}^{-1}) \tag{14}$$

where Λ is the diagonal matrix of the squares of normal model frequencies and $\mathbf{L}$ is the matrix transformation from normal to internal coordinates ($L_{ij} = \partial q_i/\partial Q_j$). Using eq 5a and eq 14, we write

$$\ln\,[\det \sigma] = \ln\,(k_{\mathrm{B}}T \det\,[\mathbf{L}\Lambda^{-1}\mathbf{L}^{+}]) = \ln\,(k_{\mathrm{B}}T \det \Lambda^{-1}) + \ln\,(k_{\mathrm{B}}T \det \mathbf{G}) \tag{15}$$

where we have used the fact that $\mathbf{L}\mathbf{L}^{+} = \mathbf{G}$. Substituting from eq 15 into eq 13, we find that the change in the configurational entropy is given by

$$\Delta S_q{}^{\mathrm{c}} = k_{\mathrm{B}} \ln \frac{\prod_{i=1}^{3N-6} \omega_i(\mathrm{a})}{\prod_{i=1}^{3N-6} \omega_i(\mathrm{b})} + \frac{1}{2}k_{\mathrm{B}} \ln \left[\frac{\det \mathbf{G}^{\mathrm{b}}}{\det \mathbf{G}^{\mathrm{a}}}\right] \tag{16}$$

$$= \Delta S_{\mathrm{vib}} + \frac{1}{2}k_{\mathrm{B}} \ln \left[\frac{\det \mathbf{G}^{\mathrm{b}}}{\det \mathbf{G}^{\mathrm{a}}}\right] \tag{17}$$

Thus the change in the configurational entropy in the harmonic approximation is equal to the vibrational entropy change plus the contribution to the entropy from the change in the Jacobian $\mathbf{G}$ evaluated at the two equilibrium conformations. There is no contribution to $\Delta S_q{}^{\mathrm{c}}$ from vibration–rotation coupling when the system normal modes obtained from a harmonic analysis are used to evaluate σ (eq 15). When the rotation–vibration coupling is neglected, as it is for the standard harmonic oscillator, or as it can be for the quasi-harmonic oscillator when the coupling is small, the explicit contribution of the rotational entropy change to $\Delta S_q{}^{\mathrm{c}}$ can be obtained. The determinant g for the complete transformation from $3N$ Cartesian to $3N$ generalized coordinates for conformation a is given by

$$g^{\mathrm{a}} = \det \mathbf{I}^{\mathrm{a}}/\det \mathbf{G}^{\mathrm{a}} \tag{18}$$

where $\mathbf{I}$ is the moment of inertia tensor for conformation a. Substituting eq 18 into eq 17, we obtain

$$\Delta S_q{}^{\mathrm{c}} = \Delta S_{\mathrm{vib}} + \frac{1}{2}k_{\mathrm{B}} \ln \left[\frac{\det \mathbf{I}^{\mathrm{b}}}{\det \mathbf{I}^{\mathrm{a}}}\right] + \frac{1}{2}k_{\mathrm{B}} \ln\,(g^{\mathrm{a}}/g^{\mathrm{b}}) = \Delta S_{\mathrm{vib}} + \Delta S_{\mathrm{rot}} + \frac{1}{2}k_{\mathrm{B}} \ln\,(g^{\mathrm{a}}/g^{\mathrm{b}}) \tag{19}$$

In the previous work[7] the discrepancy in the standard harmonic results between $\Delta S_q{}^{\mathrm{c}}$ and the sum $\Delta S_{\mathrm{vib}} + \Delta S_{\mathrm{rot}}$ was ascribed to the breakdown of the rigid rotator approximation, the presence of rotation–vibration coupling, or the variation in the Jacobian in the transformation from Cartesian to internal coordinates. However, from eq 19, which has been derived within the framework of the standard harmonic approximation, it is apparent that the difference between the configurational entropy change and the sum of the vibrational plus rotational entropy change is a term that involves the conformational dependence of g. Since g depends only on bond lengths and angles,[9,10] the change in g with conformation is expected to be very small and can be neglected in eq 19, so that

$$\Delta S_q^{\,c} \approx \Delta S_{\text{vib}} + \Delta S_{\text{rot}} \tag{20}$$

We make two further points concerning the harmonic and quasi-harmonic methods for evaluating the configurational entropy. First, if the complete partition function Z_{vib} (eq 9a) for the internal Hamiltonian is used to evaluate the entropy change, instead of the reduced configurational integral Z_c (eq 9b), the factors depending on det **G** and det $\mathbf{G}^{-1}$ cancel and we have simply in the rigid rotator approximation with the neglect of rotation–vibration interaction

$$k_B \ln\,[Z_{\text{vib}}{}^{b}/Z_{\text{vib}}{}^{a}] = \Delta S_q^{\,c} + \tfrac{1}{2}k_B \ln\left[\frac{\det \mathbf{G}^{a}}{\det \mathbf{G}^{b}}\right] = \Delta S_{\text{vib}} \tag{21}$$

This is the result we must obtain for any model Hamiltonian that is quadratic in the internal coordinates and momenta. Equations 14–21 are also valid for the quasi-harmonic approximation when **F** is calculated from eq 5a and eq 5b is calculated from the results of a molecular dynamics simulation. The effective (quasi-harmonic) normal mode frequencies, eigenvectors, and **G** matrix elements will of course be different from the values obtained from the standard normal mode analysis (see Conclusions).

Application

We have previously described a study of the full molecular dynamics of an isolated α-helix as a function of temperature between 5 and 300 K and compared the results obtained with those for the same system in the harmonic approximation.[11] The system considered is α-helical decaglycine. The details of the model, including the empirical potential function, have been presented previously.[12] A series of temperatures between 5 and 300 K was studied. For each temperature trajectories were calculated by solving simultaneously the classical equations of motion for the atoms of which the helix is composed. A comparison of the configurational entropy $S_q^{\,c}$ (eq 12) for the decaglycine molecule obtained in the harmonic and quasi-harmonic approximations has been carried out. We have used the results of the molecular dynamics simulation and of a standard normal mode analysis to construct σ in the harmonic and quasi-harmonic approximation. In the harmonic approximation the elements of σ have the form[7,12]

$$\sigma_{ij}{}^{\text{HA}} = \langle (q_i - \langle q_i\rangle)(q_j - \langle q_j\rangle)\rangle = k_B T \sum_{k=1}^{3N-6} \frac{\alpha_{ik}\alpha_{jk}}{\omega_k{}^2} \tag{22}$$

where α_{ik} is the projection of the kth normal coordinate onto the ith internal coordinate. In the quasi-harmonic approxmation, the elements of σ are constructed from the molecular dynamics trajectory:

$$\sigma_{ij}{}^{\text{QHA}} = \frac{1}{n}\sum_{t=1}^{n}(q_i{}^t - \langle q_i\rangle)(q_j{}^t - \langle q_j\rangle) \tag{23}$$

where $\langle q_i\rangle$ is the average value of q_i along the trajectory, $q_i{}^t$ is the value of q_i and time t, and n is the number of time points sampled. The configurational entropy difference between the harmonic and quasi-harmonic models for the system is then

$$\Delta S_q^{\,c} = \frac{k_B}{2} \ln\left[\frac{\det \sigma^{\text{QHA}}}{\det \sigma^{\text{HA}}}\right] \tag{24}$$

Table I

T, K	ΔS[a]	$T\Delta S$[b]	$\Delta S/S_{\text{vib}}$,[c] %
5	0.45	2.2×10^{-3}	
100	16.11	1.6	
300	43.91	13.17	63

[a] $\Delta S = S_{\text{QHA}} - S_{\text{HA}}$, the difference between S calculated in the quasi-harmonic approximation and the harmonic approximation. Entropy units, cal/(mol K). [b] kcal/mol. [c] The difference between the quasi-harmonic and the harmonic approximations to the entropy ΔS divided by the total absolute classical vibrational entropy, $S_{\text{vib}} = \sum_{i=1}^{3N-6} k_B(1 - \ln\,(h\omega_i/kT))$, for the α-helix. Since there are significant quantum corrections to the absolute classical vibrational entropy,[7] only the high-temperature value is listed.

The results are presented for three temperatures, 5, 100, 300 K, in Table I. At the very low temperature (5 K), the entropy different $\Delta S_q^{\,c}$ is negligible. The harmonic approximation is essentially exact since at this low temperature the classical trajectory is confined to the quadratic portion of the potential surface close to the minimum-energy conformation. In contrast to the low-temperature values for the entropy, at 300 K the harmonic approximation substantially underestimates the entropy ($\Delta S_q^{\,c}$ = 43.9 eu). The entropy difference at 300 K is greater than 60% of the classical estimate for the absolute vibrational entropy of the helix in the harmonic approximation. The increased entropy of the α-helix due to anharmonicity is estimated in the classical limit to stabilize the helix on the order of 10 kcal/mol at 300 K with respect to the harmonic model.

Conclusions

There is a growing interest in using molecular mechanics to model the binding of ligands to proteins and nucleic acids and to study problems associated with drug design. Central to this effort is the development of approximate methods for calculating thermodynamic properties.[7,9,13–16] The results of the model calculations reported in this paper demonstrate that at room temperature, anharmonicity can have a substantial effect on the thermodynamics of biopolymers. Thus, caution will have to be used in the interpretation of theoretical studies of ligand binding based on the standard normal mode analysis for the vibrational entropy, although it is possible that anharmonic effects will cancel in part in the entropy change between free and bound species. The quasi-harmonic approximation to the potential described previously[7] utilizes molecular dynamics simulations for partially incorporating anharmonic effects in the calculation of statistical thermodynamic properties. The extension of the method as proposed here to the construction of temperature-dependent effective quadratic Hamiltonians with associated quasi-harmonic frequencies and eigenvectors is expected to be useful for studying the classical and quantum statistical thermodynamics and spectroscopy of large molecular systems. The quasi-harmonic model has been applied to the study of the low-frequency elastic properties of a protein[17] and to the calculation of vibrational spectra from Monte Carlo simulations on multidimensional anharmonic potential surfaces.[18] Within the quasi-harmonic oscillator model, quantum corrections to the thermodynamic properties are easily evaluated from standard formulas for the thermodynamic quantities as a function of the density of states, although for the ligand binding problem quantum effects may be small since the conformational changes associated with binding are expected to have the largest effect on the low-frequency (classical) modes.

The quasi-harmonic oscillator model we have developed for evaluating the thermodynamics of biomolecules is in some respects similar to the recently proposed method of Wilson et al.[19] for evaluating thermodynamic and quantum effects from spectral decompositions of correlation functions based on classical molecular dynamics simulations. The derived spectral densities constitute temperature-dependent effective harmonic models for the anharmonic systems. The quasi-harmonic potential approximation and the extension to the calculation of normal modes and frequencies proposed here have the advantage, however, that the approximations involved in the calculations can be systematically improved. In a forthcoming paper[20] it is demonstrated that the quasi-harmonic potential approximation constitutes the first term in a series expansion of the classical configurational distribution function in the moments of the distribution; the convergence properties of the expansion are under study for a variety of model systems, including the α-helix. With regard to quantum effects, Friesner and Levy have demonstrated[21] that the quasi-harmonic oscillator model provides an optimized reference system for the evaluation of discretized path integrals from which it is possible to compute accurate quantum mechanical expectation values. The evaluation of statistical thermodynamic quantities for large molecular systems such as biomolecules poses difficult computational problems which requires the judicious application of approximations. For proteins with well-defined conformations, the quasi-harmonic oscillator model provides a very powerful approach for studying the thermodynamics. Applications of the method to the binding of a ligand to a protein[22] and to the study of protein fluctuations[23] are under way.

Acknowledgment. We thank Robert Sheridan and Miguel Zuniga for help with the calculations. This work has been supported by a grant from the National Institutes of Health (Grant GM30580). R.M.L. is an Alfred P. Sloan Fellow and the recipient of a NIH Research Career Development Award. J.N.K. is a Camille and Henry Dreyfus Teacher-Scholar.

References and Notes

(1) Lumry, R.; Rajendev, S. *Biopolymers* **1970**, *9*, 1125.
(2) Hinz, H. J.; Shaio, D. D. F.; Sturtevant, J. M. *Biochemistry* **1971**, *10*, 1347.
(3) Ross, P.; Subramanian *Biochemistry* **1981**, *20*, 3101.
(4) Sturtevant, J.; Velicelebi *Biochemistry* **1981**, *20*, 3091.
(5) Privalov, P. L. *Adv. Protein Chem.* **1979**, *33*, 167.
(6) Sturtevant, J. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 2236.
(7) Karplus, M.; Kushick, J. *Macromolecules* **1981**, *14*, 325.
(8) Wilson, E. B.; Decius, J. C.; Cross, P. C. "Molecular Vibrations"; McGraw-Hill: New York, 1955.
(9) Go, N.; Scheraga, H. A. *J. Chem. Phys.* **1969**, *51*, 4751.
(10) Fixman, M. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 3050.
(11) Levy, R. M.; Perahia, D.; Karplus, M. *Proc. Natl. Acad. Sci. U.S.A.* **1982**, *79*, 1346.
(12) Levy, R. M.; Karplus, M. *Biopolymers* **1979**, *18*, 2465.
(13) Lifson, S.; Warshel, A. *J. Chem. Phys.* **1968**, *49*, 5116.
(14) Go, N.; Scheraga, H. A. *Macromolecules* **1976**, *9*, 535.
(15) Hagler, A. T.; Stern, P. S.; Sharon, R.; Becker, J. M.; Naider, F. J. *J. Am. Chem. Soc.* **1979**, *101*, 6842.
(16) Meirovitch, H. *Chem. Phys. Lett.* **1977**, *45*, 389.
(17) Levy, R. M.; Srinivasan, A. R.; Olson, W.; McCammon, J. A. *Biopolymers*, in press.
(18) Levy, R. M.; Rojas, O.; Freisner, R. *J. Phys. Chem.*, in press.
(19) Berens, P. H.; MacKay, D. H.; White, G.; Wilson, J. *J. Chem. Phys.* **1983**, *79*, 2375.
(20) Levy, R. M.; Rojas, O.; Szabo, A., to be published.
(21) Friesner, R. A.; Levy, R. M. *J. Chem. Phys.* **1984**, *80*, 4488.
(22) Keepers, J.; Levy, R. M., to be published.
(23) Brooks, B.; Karplus, M., to be published.

High-Temperature Dielectric Relaxation in α- and γ-Phase Poly(vinylidene fluoride)

Peggy Cebe[†] and David T. Grubb*

Department of Materials Science and Engineering, Cornell University, Ithaca, New York 14853. *Received July 26, 1983*

ABSTRACT: The dielectric response of poly(vinylidene fluoride) films and single-crystal mats has been measured from room temperature to the melting point in the frequency range 200–10 000 Hz. Samples studied were α-phase melt-crystallized films, isothermally crystallized films of mixed γ and α phase, and mats of solution-crystallized γ and α phase. For α-phase films, observed decreases in dielectric constant with increasing temperature have been correlated with changes in crystallinity due to melting. Ion removal and annealing are shown to have very different effects on the dielectric behavior, though both involve the same heat treatment. In γ-phase films, the dielectric constant increases with increasing temperature to high values. Single-crystal mats exhibit a crossover from an α-dominated relaxation at lower temperature to γ-dominated behavior at high temperature. Very high values of dielectric constant and loss are obtained from mats and from films crystallized isothermally in an electric field, due to a relaxation of the polar γ crystals near their melting point.

1. Introduction

Poly(vinylidene fluoride), PVF$_2$, is a semicrystalline polymer of more than usual complexity. The molecule is highly polar, and in three of the five crystal structures known to exist, the molecular dipoles are parallel, giving polar crystals and electrically active materials. The structure and properties of PVF$_2$ have been summarized in a recent review of Lovinger.[1] The dielectric properties of the crystal forms are generally very different, although some forms are difficult to distinguish structurally. Further, it is often not possible to obtain samples containing only the crystal modification of interest. Even if this can be achieved, the material is only 50% crystalline, so it is always a composite of crystal and amorphous regions, an inhomogeneous dielectric. The amorphous regions of the polar material normally contain some ionic species, which may be free to move at high temperatures. One last complication is that the molecule normally contains a fraction of head-to-head units that strongly affect the stability of the various crystal forms.

Extensive dielectric studies have been performed on the α phase, which is produced by cooling the melt. Investigators identified two[2,3] and then three relaxations,[4–7] one above room temperature and two below. The high-tem-

---

[†] Present address: Jet Propulsion Laboratory, Pasadena, CA 91109.

0024-9297/84/2217-1374$01.50/0