Conformational Distinguishability of Medium Cycloalkanes in Crystals via Inelastic Neutron Scattering

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This paper begins an exploration of the use of the combination of DFT computations with experimental inelastic neutron scattering (INS) spectra as a method for establishing what conformation is present in a molecular crystal at low temperature. Presented here are INS spectra of a series of medium-sized cycloalkanes: C_6H_{12}, C_7H_{14}, C_8H_{16}, $C_{10}H_{20}$, $C_{12}H_{24}$, and $C_{14}H_{28}$. Optimized geometries and normal mode calculations were performed at B3LYP/6-311G(d,p) on the lowest energy conformations (i.e., those thermally accessible at the experimental temperature of 30 K). The calculated and observed spectra were analyzed for the best fit from each set of conformers, allowing a prediction of the dominant conformation in a conformationally rich system. For each cycloalkane, the calculated spectrum for the lowest energy conformer shows good agreement with experiment while the higher energy conformations have a much poorer fit. With little ambiguity, the lowest energy conformer is therefore predicted to be the dominant conformation, consistent with the diffraction data available for C_6H_{12}, $C_{10}H_{20}$, $C_{12}H_{24}$, and $C_{14}H_{28}$. These results indicate that INS spectroscopy may be a useful tool in determining the dominant conformation in a crystal lattice in cases such as this in which the intermolecular interactions are weak and the different conformers are calculated to have distinguishable spectra. Such an analysis is applied to the cases of C_7H_{14} and C_8H_{16} for which no low-temperature X-ray analysis is available. Clear structure predictions result, and the conformer observed is that computed to be of lowest energy for the molecule in isolation.

Introduction

The conformation that a molecule adopts in its crystalline form may differ from its lowest energy conformation in gas or solution phase. An example is the planar conformation of biphenyl in the room-temperature crystal.[1,2] Such a change in conformation in going from the isolated molecule to the crystal is a result of the crystal packing forces in addition to the relative energies of the molecular conformations. Even weak intermolecular forces will produce this effect if the conformational space is sufficiently populated with low-energy alternatives to the global minimum. In some cases, a variety of molecular conformations and crystal packing arrangements are exhibited in what has been called conformational polymorphism.[3−5] This effect is relevant in the evaluation of the ability of various computational methods to reproduce experimental molecular geometry.

In principle, the effect of crystal packing forces is included in periodic computational methods. Such treatments are needed when detailed structure predictions are of interest.[6] However, there are cases in which what is desired is a description of the conformation of a molecule in a crystal at an approximate level but with sufficient specificity that alternative conformations can be eliminated. Applications of this type include the interpretation of solid-state NMR data, analysis of powder diffraction data for flexible molecules,[7−9] and detection and interpretation of phase transitions or polymorphism.

The role of crystallography in this field, usually the premier method in conformational analysis, is compromised by difficulties in obtaining and handling suitable crystals, the presence of multiple phase transitions, and the presence of crystal disorder. There is also the ever-present, but here more obvious, issue that the lowest energy conformation for the isolated molecule may not be the one present in the crystal even at low temperature due to the fact that crystal forces may favor a higher energy conformation. In this case, an isolated molecule calculation of relative conformational energies will not provide an accurate prediction of the solid-state conformation. Thus, if no crystal structure is known, another solid-state experimental method is necessary to confirm the molecular conformation in the solid state. For example, of the cycloalkanes from C_6H_{12} to $C_{14}H_{28}$ only four, C_6H_{12}, $C_{10}H_{20}$, $C_{12}H_{24}$, and $C_{14}H_{28}$, have known crystal structures.

Vibrational spectroscopy has often been used as a method of crystal structure analysis[10,11] to provide information on the number of molecules per unit cell, the site symmetry, and, in some cases, the conformational state. Vibrational data has the great advantage over NMR or diffraction data of providing a near instantaneous and local picture of the nuclear dynamics which represents disorder as a sum of contributions rather than dynamically or spatially averaged. Recently, it has become routine to compute molecular vibrational frequencies with good precision. This permits a more comprehensive use of vibrational information in crystal structure analysis because the results of calculations for various conformations can be compared with experiment. In this respect, inelastic neutron scattering (INS) offers several advantages over IR and Raman methods. The major advantage is the ability to compute the spectral intensities

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directly from the normal mode eigenvectors with no need to involve the response of the electrons to the nuclear motion. This permits a more facile and reliable quantitative comparison between theory and experiment. In fact, the theory by which one computes the INS spectral intensity from a set of normal-mode eigenvectors is in many respects similar to that used for the computation of diffraction data within the usual “thermal parameter” approximation. They both depend on the harmonic approximation. Diffraction analysis assumes independence of the atomic motions, but incoherent INS does not.

INS spectra have no selection rules and usually exhibit features with good resolution in the frequency region from 100 to 800 cm^{-1} where different conformations of the same molecule differ in their vibrations in significant ways. INS spectroscopy is primarily useful when applied to polycrystalline samples at low temperature. The temperature used is usually 15−30 K, below that usually used even for “low-temperature” X-ray studies. This means that there is always the possibility that the molecular conformation present in the low-temperature crystal is distinct from that observed in available X-ray studies. This does not appear to be the case for any of the molecules investigated here. The quantitative comparison between the computed and observed INS spectra presented here demonstrates that only one conformation is present in detectable amounts in these crystals at the temperatures used to obtain the INS spectra.

The present paper is an exploration of whether this method for conformational analysis works for a case where the intermolecular interactions are weak and the conformational space is complex but denumerable. In some of the cases investigated, the crystalline conformation is known; in others, it is not. The key issue is the extent to which alternative conformations can be eliminated as possibilities.

The medium ring cycloalkanes have a long history as a testing ground for empirical treatments of conformational energetics and interconversions.[12−16] The cyclo C_7−C_{10} compounds have recently received extensive treatment by post-Hartree−Fock ab initio methods.[17,18] The major interest and challenge of these studies stem from the presence of multiple low-energy minima on the conformational energy surface. Vibrational spectroscopy is a useful technique in this area because it is able to report on the presence of each of the multiple conformations as distinct signals.[19−22] Solid-state NMR[23−27] has played an important role in these studies because of its ability to detect phase transitions, to distinguish between static and dynamic disorder, and to detect the presence of minor species.

In the present study, we show that the INS spectra computed[28] for the conformation that is predicted to be lowest in energy by the B3LYP/6-311G(d,p) method agree with the experimental INS spectrum obtained at $T < 30$ K for each of the six cycloalkanes. This is also the conformation that is observed in the four cases for which a crystal and molecular structure is available. We further show that the INS spectra computed for the other low-energy conformations of these cycloalkanes do not agree with the experimental spectra. The differences between the observed spectra and those computed for the “correct” and “incorrect” conformations are significant.

These conformational and spectral calculations are performed for isolated cycloalkane molecules. The observation that the computed spectrum agrees with the experimental spectrum reflects the fact that intermolecular forces between alkanes are weak. The most obvious differences between the conformers occur in the very low-frequency region of the spectrum. The deformations found in the low-frequency part of the spectrum are presumably those susceptible to intermolecular interactions and mixing or overlap with external (phonon) degrees of freedom. Such effects can be treated using periodic DFT methods, but this requires that a crystal structure be known. We know from previous work[6,29] that the residual differences between the computed and observed spectra for the correct conformation are due primarily to the lack of inclusion of the intermolecular interactions in the dynamical treatment rather than to deficiencies in the DFT method. The present method permits the determination of molecular structure in a polycrystalline low-temperature crystal sample without obtaining or interpreting diffraction data. It is also applicable when a mixture of conformations is present in a crystal.

Materials and Methods

The INS spectra were measured using the time-of-flight spectrometer TOSCA at ISIS, the pulsed neutron source at Rutherford Appleton Laboratories. The spectra were collected for samples at approximately 25 K over the range of 4−500 meV (32−4000 cm^{-1}) with a resolution of 1.5−3.0% of the energy transfer ($\Delta\omega/\omega$).[30] The backscattering spectra are chosen over the forward scattering spectra for presentation due to lower background levels and fewer effects from multiple scattering events.

Cycloheptane (98%), cyclooctane (99+%), and cyclodecane (98%) were obtained from Aldrich Chemical Co. and used as received. Cyclododecane and cyclotetradecane were supplied by ChemSampCo, the latter rented, not purchased. The cyclohexane spectrum can be found in an index of spectra accessible from the TOSCA website.[31]

The output of the DFT calculations was used as input for the aClimax[32] program which calculates INS transitions for 1−10 vibrational quanta of each of the harmonic modes and their combinations, incorporating instrumental bandwidth and phonon modes in a spectrum that is designed for ease of comparison with experiment. These combinations and overtone transitions constitute a rising intensity in the spectra at high energy.

Inelastic Neutron Scattering Analysis. The observed INS spectrum can be described by the following scattering law, with summation over all atoms l for n quanta transitions as written in eq 1.[33−35]

$$S^{\bullet}(\mathbf{Q},\omega_\nu)_l^n = \frac{\sigma_l}{4\pi}\frac{[\mathbf{Q}\cdot{}^{\nu}\mathbf{u}_l]^{2n}}{n!}\exp\left(-\mathbf{Q}\cdot\sum_{\nu}{}^{\nu}\mathbf{u}_l\coth\left(\frac{\hbar\omega_\nu}{2k_\mathrm{B}T}\right)\right)^2 \quad (1)$$

The neutron undergoes a change in momentum $\mathbf{Q}$ upon the excitation of molecular vibration ν of frequency ω_ν. The neutron cross section for the incoherent scattering from atom l is σ_l. This cross section is roughly 80 barns (1 barn $= 10^{-24}$ cm^2) for hydrogen, 2 barns for deuterium, and 10^{-3} barns for natural abundance carbon. Therefore, in the molecules under consideration here, hydrogen is effectively the only atom contributing to the INS spectrum. The temperature-dependent Debye−Waller factor is the exponential term in eq 1. At the cryogenic temperatures used in these studies, $\coth(\hbar\omega_\nu/2k_\mathrm{B}T)$ is very near unity. The displacement of atom l upon the excitation of this normal mode is ${}^{\nu}\mathbf{u}_l$. The quantity calculated using DFT or ab initio methods is the coefficient of the eigenvector for that mode ${}^{\nu}\mathbf{c}_l$, which is related to the displacement by the relationship, ${}^{\nu}\mathbf{u}_l = {}^{\nu}\mathbf{c}_l/(\omega_\nu m_l/\hbar)^{1/2}$, where the vibrational eigenvectors are normalized such that $\sum_l {}^{\nu}\mathbf{c}_l^2 = 1$.

Thus, the intensity of a vibrational peak in an INS spectrum is determined by the magnitude of the hydrogen displacements upon excitation of the normal mode. This information is

TABLE 1: Values for an *F* Distribution in which $F(j,j) = \chi^2_A/\chi^2_B$ and $j = m - n$, Where *m* Is the Number of Data Points (vibrational frequencies) and *n* Is the Number of Adjustable Parameters (linear slope) in a Linear Fit of Observed to Calculated Vibrational Frequencies[a]

$F(j,j)$	3.44	2.98	2.69	2.4	2.12	1.84	1.69	1.53	1.35	1
j	8	10	12	15	20	30	40	60	120	∞

[a] A value of $F(j,j) = \chi^2_A/\chi^2_B$ greater than that listed in the table[38] allows model (conformer) A to be discarded in favor of model (conformer) B with 95% confidence.

provided in the eigenvector description of a DFT normal mode analysis, and in this respect, it is straightforward to compare the calculated and observed INS transition intensity. If the eigenvectors calculated for a given conformation are not a good description of the conformer present in the experimental sample, then this will be reflected in the relative normal mode intensities.

The best way to compare the observed and calculated conformers is to compare both the frequencies and intensities. The drawback in the comparison of the relative intensities is in the error presented by the counting statistics in the observed spectrum. Instead of arbitrarily subtracting diffuse spectral features to identify experimentally observed peaks, the diffuse spectral contributions can be simulated using a well-established formalism.[35] In theory, the contributions to the diffuse spectral intensity underlying the sharper vibrational transitions are well accounted for: these include phonon modes as well as molecular overtones and combination bands. Indeed, the aClimax[32] program calculates all of these contributions. In the favorable case of the hydrocarbon dodecahedrane ($C_{20}H_{20}$), it has been shown[6] that an empirical treatment of the phonon spectrum leads to a quantitative description of the diffuse overtone and combination features that manifest in an apparent "baseline." This case is particularly favorable because of the cubic nature of the crystal which makes approximations to the tensor nature of the overtone and combination intensities strictly valid.[36] For noncubic crystals, the treatment of aClimax is approximate. Ultimately, the "baseline" calculation is limited by the harmonic approximation. Thus, if the calculated and experimental spectra are properly scaled relative to one another and subtracted, then the residual will have contributions not only due to an inaccurate normal mode description but also due to an inaccurate description of the overtone and combination bands, particularly those involving phonon modes.

Therefore, in this study, we quantitatively compare only the frequencies and not the relative intensities of the calculated and observed spectra. The spectral intensities are used to establish which calculated transitions should be paired with which observed feature and to establish when two transitions overlap. For these molecules, this approach to the analysis appears to be sufficient to distinguish among the possible conformers present in the experimental sample. The calculated vibrational frequencies are compared with the experimental vibrational frequencies (over the range of 0−1800 cm^{-1}) that best match the intensity observed in the INS spectra. These values are fit to a linear function, $y = P1x + b$, with the y-intercept forced to zero, based upon the assumption that a DFT calculation for the same conformer observed in the experiment would require only a multiplicative scaling factor to acquire a best fit. The chi-square (χ^2) values of these fits, computed on the basis of unit weight, are compared for each conformation. That with the lowest χ^2 value is most similar to the observed spectrum. The quality of the agreement of each conformer is presented as a ratio with the lowest χ^2 value in the denominator. To determine if these differences are statistically significant, one can utilize an *F* distribution,[37,38] $F(j,j)$, where *m* data points and *n* adjustable parameters give $j = m - n$ (see Table 1). If the ratio χ^2_A/χ^2_B is greater than $F(j,j)$, then model (conformer) B can be selected over model (conformer) A with 95% confidence ($P = 0.05$). For each conformation A, the ratio χ^2_A/χ^2_B is presented with B as the conformer with the lowest χ^2 value.

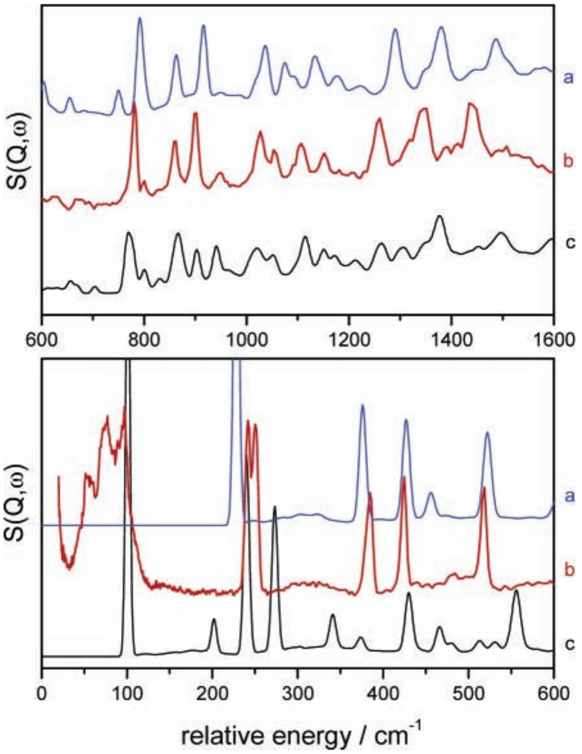

Figure 1. Chair (a, blue) and twist boat (c) cyclohexane spectra, calculated with B3LYP/6-311G(d,p) and simulated using aClimax, compared with the experimental cyclohexane spectrum (b, red).

Results

Cyclohexane. There are four crystal phases of cyclohexane. The phase likely observed in these studies is referred to as phase II and is stable below 186 K[39] in the sense that no phase transition has been detected below 186 K. The molecule sits in a centrosymmetric site (as confirmed by IR and Raman spectroscopy). At 115 K, the crystal is monoclinic, $a = 11.23(2)$, $b = 6.44(2)$, $c = 8.20(2)$ Å, $\beta = 108.83(17)°$ with $Z = 4$ and is in space group Cc or $C2/c$.[39] The molecular structure adopts a chair conformation with D_{3d} symmetry. NMR studies show that the lattice is rigid at 150 K and below, but above 150 K, the crystal exhibits orientational jumping behavior.[40] The packing of the phase II crystal is fairly loose, consistent with the orientational rearrangement above 150 K. An isolated molecule calculation is therefore probably an appropriate model for the solid-state spectrum, at least for cyclohexane.

The frequencies and relative intensities calculated for the chair cyclohexane conformer agree quite well with the INS spectrum collected by Parker[31] as demonstrated in Figure 1. Those calculated for the twist boat conformer are not in such close agreement with the experiment. The observed frequencies are compared with the calculated frequencies for both conformers, with the results presented in Table 2. The χ^2 value for the twist

TABLE 2: Results of Calculated and Observed Cyclohexane Frequencies Fit to a Linear Function with the Intercept Forced to Zero: $y = P1x$[a]

cyclohexane	$P1$	$P1$ error	χ^2	relative χ^2
chair (D_{3d})	0.979	0.002	153	1.0
twist boat (D_2)	0.979	0.003	480	3.1

[a] For this set of spectra, $j = 35$ with $F(30,30) = 1.8$ required to determine the presence of one conformer over another.

TABLE 3: Relative Energies (kcal/mol) Calculated for the Conformations of Cycloheptane

cycloheptane	MP2/ 6-311++G(d,p)[17]	CCSD/ 6-311++G(d,p)[17]	B3LYP/ 6-311G(d,p)[a]
twist chair	0	0	0.0
chair	1.1	0.9	0.8
boat	3.1	3.3	3.6
twist boat	3.2	3.3	3.6

[a] This work.

TABLE 4: Results of Calculated and Observed Cycloheptane Frequencies Fit to a Linear Function with the Intercept Forced to Zero: $y = P1x$[a]

cycloheptane	$P1$	$P1$ error	χ^2	relative χ^2
twist chair (C_2)	0.972	0.002	175	1.0
boat (C_S)	0.991	0.003	580	3.3
chair (C_S)	0.978	0.002	329	1.9
twist boat (C_2)	0.974	0.003	437	2.5

[a] For this set of spectra, $j = 41$ with $F(40,40) = 1.7$ required to determine the presence of one conformer over another.

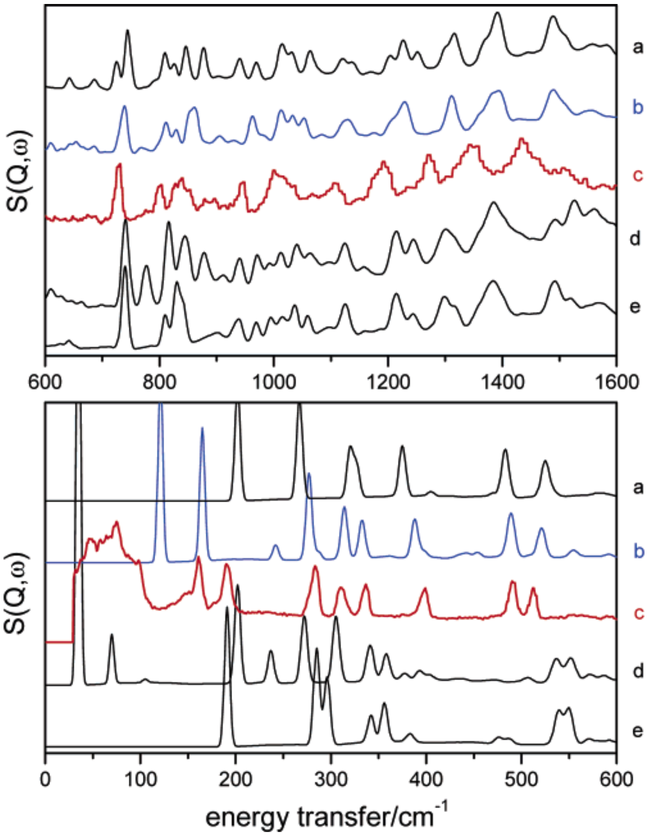

Figure 2. Chair (a), twist chair (b, blue), boat (d), and twist boat (e) cylcoheptane spectra, calculated with B3LYP/6-311G(d,p) and simulated using aClimax, compared with the experimental cycloheptane spectrum (c, red). The spectra displayed in the higher frequency range are magnified by a factor of 2 relative to those in the low-frequency panel.

TABLE 5: Relative Calculated Energies (kcal/mol) for the Conformations of Cyclooctane

cyclooctane	MP2/ 6-311++G(d,p)[17]	CCSD/ 6-311++G(d,p)[17]	B3LYP/ 6-311G(d,p)[a]
boat chair	0.0	0.0	0.0
twist boat chair	1.5	1.6	1.6
crown	2.2	1.5	0.3
boat boat	4.0	4.0	3.0

[a] This work.

TABLE 6: Results of Calculated and Observed Cyclooctane Frequencies Fit to a Linear Function with the Intercept Forced to Zero: $y = P1x$[a]

cyclooctane	$P1$	$P1$ error	χ^2	relative χ^2
boat chair (C_S)	0.973	0.002	174	1.0
crown (D_{4d})	0.971	0.004	864	5.0
boat boat (D_{2d})	0.982	0.005	1653	9.5
twist boat chair (C_2)	0.977	0.002	308	1.8

[a] For this set of spectra, $j = 49$ with $F(40,40) = 1.7$ required to determine the presence of one conformer over another.

boat conformation is 3.1 times greater than that for the chair conformation, indicating that the predominant conformation in this crystal is the chair. The DFT calculations predict that the energy of the cyclohexane twist boat conformation is 6.3 kcal/mol ($\geq 100kT$ at 30 K) greater than that of the chair conformer, consistent with the interpretation that the chair conformation is that observed in the INS spectra. The heat of sublimation of cyclohexane is ca. 7 kcal/mol.[41] For the twist conformation to be the most stable form in the crystal, the crystal packing energy would have to be nearly twice as large for this higher energy conformer.

Cycloheptane. The crystal structure of cycloheptane is, to our knowledge, unknown. Thomas et al.[42] have studied the X-ray structural data of many cycloheptane derivatives with the aim to determine the most likely conformation adopted by the unsubstituted cycloheptane. Most commonly, although not exclusively, these cycloheptane derivatives are found in the twist chair conformation.[42,43] The twist chair conformation is also predicted from isolated molecule calculations[17,44−46] to be the most stable. The DFT relative energies are in good agreement with those calculated previously[17] at CCSD and MP2 levels of theory as presented in Table 3.

INS spectra were calculated for the boat, chair, twist boat, and twist chair conformations, being those calculated by Wiberg[17] to have the lowest energy. From these results, the INS intensity is displayed in Figure 2 with the experimental spectrum. The observed and calculated frequencies are compared for each conformer, and the results of the analysis are presented in Table 4. The χ^2 values for each conformation relative to the twist chair are greater than the $j = 41$ critical value of 1.7, indicating the twist chair spectra best match the observed spectra.

Cyclooctane. There has yet to be a crystal structure reported for cyclooctane itself. Huang et al.[22] studied solid-state cyclooctane using optical spectroscopy. They studied three stable phases (I, II, and III) and one metastable phase (III′). Phase III is stable at 166 K and below and is the phase most likely observed in the INS spectra. Srinivasan et al.[47] studied derivatives of cyclooctane via X-ray crystallography and found that cyclooctane crystals (at 93 K) are most likely to adopt a boat chair conformation. Isolated molecule calculations in this study and others[17] predict the boat chair to be the most energetically favorable conformation (see Table 5). Indeed, the statistical analysis of B3LYP/6-311G(d,p) calculated frequencies with the INS measurements of cyclooctane at 25 K strongly suggests that the sample is found in the boat chair conformation. All of

TABLE 7: Relative Calculated Energies (kcal/mol) for the Conformations of Cyclodecane

cyclodecane	MP2/ 6-311++G(d,p)[17]	CCSD/ 6-311++G(d,p)[17]	B3LYP/ 6-311G(d,p)[a]
boat chair boat	0.0	0.0	0.0
twist boat chair chair	0.4	0.7	1.2
twist boat chair	0.7	0.6	0.9
buckled crown	1.6	2.0	2.4
crown	1.6	2.2	2.9

[a] This work.

the relative χ^2 values are greater than the 1.7 required to identify the dominant conformer. The results of this comparison can be found in Table 6. The observed and calculated spectra are presented in Figure 3.

Cyclodecane. There are six cyclodecane conformations that are calculated[17] to have sufficiently similar energies as to be thermally accessible at room temperature. The energies of the lowest five are presented below (see Table 7). A number of researchers have calculated, using a variety of methods, the relative energies of cyclodecane conformers[48,49] from which the boat chair boat (BCB) conformation is predicted to be the most stable. The structure determined from X-ray diffraction near 173 K adheres to the BCB conformation[50] as does a solid-state ^{13}C NMR study.[27] The crystal structures of many cyclodecane derivatives[51,52] have been investigated with the majority found to obtain a BCB conformation in the solid state as well.

Many of the calculated frequencies do not differ greatly from one conformer to another but are clearly distinguishable as arising from different conformers. Most noticeably, the relative INS intensities (Figure 4) are distinct and are useful in determining the presence of one conformer over another. In the case of the B3LYP/6-311G(d,p) cyclodecane frequency calculations, the conformations exhibit similar spectra but the one with the vibrational frequencies and intensity pattern that matches the observed spectrum most closely is that of the BCB conformer,

TABLE 8: Results of Calculated and Observed Cyclodecane Frequencies Fit to a Linear Function with the Intercept Forced to Zero: $y = P1x$[a]

cyclodecane	$P1$	$P1$ error	χ^2	relative χ^2
boat chair boat (C_{2h})	0.969	0.002	219	1.0
buckled crown (C_1)	0.977	0.003	574	2.6
crown (C_{2h})	0.973	0.004	1084	4.9
twist boat chair chair (C_2)	0.981	0.003	836	3.8
twist boat chair (C_2)	0.975	0.002	369	1.7

[a] For this set of spectra, $j = 63$ with $F(60,60) = 1.5$ required to determine the presence of one conformer over another with 95% confidence.

TABLE 9: Relative Calculated Energies (kcal/mol) for the Conformations of Cyclododecane

cyclododecane	MM2[54]	B3LYP/6-311G(d,p)[a]
C1 (D_4)	0.0	0.0
C2 (C_1)	1.0	2.5
C3 (C_S)	2.4	3.6

[a] This study.

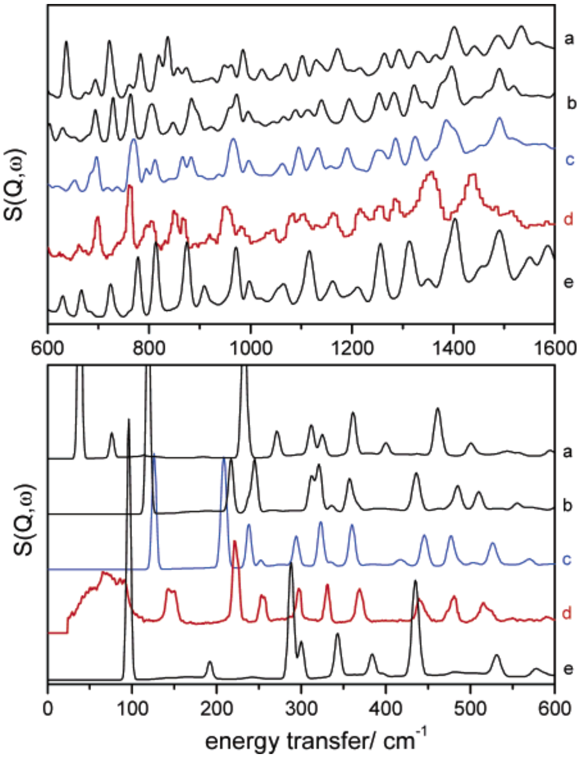

Figure 3. Boat boat (a), twist boat chair (b), boat chair (c, blue), and crown (e) cyclooctane spectra, calculated with B3LYP/6-311G(d,p) and simulated using aClimax, compared with the experimental cyclooctane spectrum (d, red). The spectra displayed in the higher frequency range are magnified by a factor of 3 relative to those in the low-frequency panel.

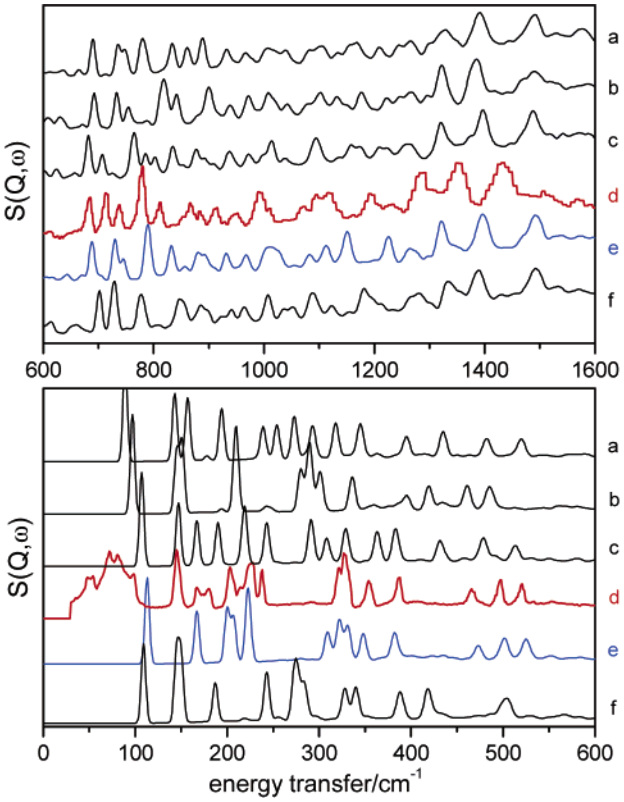

Figure 4. Buckled crown (a), crown (b), twist boat chair (c), boat chair boat (e, blue), and twist boat chair chair (f) cyclodecane spectra, calculated with B3LYP/6-311G(d,p) and simulated using aClimax, compared with the experimental cyclodecane spectrum (d, red). The spectra displayed in the higher frequency range are magnified by a factor of 3 relative to those in the low-frequency panel.

TABLE 10: Results of Calculated and Observed Cyclododecane Frequencies Fit to a Linear Function with the Intercept Forced to Zero: $y = P1x$[a]

cyclododecane	$P1$	$P1$ error	χ^2	relative χ^2
C1 (D_4)	0.972	0.001	107	1.0
C2 (C_1)	0.976	0.002	352	3.3
C3 (C_S)	1.000	0.003	1112	10.4

[a] For this set of spectra, $j = 77$ with $F(60,60) = 1.5$ required to determine the presence of one conformer over another with 95% confidence.

as is expected based on previous calculations and observations. This is reflected in the data analysis reported in Table 8 in which the χ^2 value for the BCB conformer agrees significantly better with experiment than the other conformers studied and the relative χ^2 values are greater than the value of 1.5 needed to confirm the presence of one conformer over another.

Cyclododecane. The crystal structure of cyclododecane at room temperature is monoclinic, in space group $C2/m$, with two molecules per unit cell.[53] The crystal consists of a single conformer that could have either D_2 or D_4 symmetry. The crystal undergoes a phase transition in the 173−153 K range,[53] the crystallographic details of which are not known. The solid-state ^{2}H NMR[25] and the ^{13}C NMR[24] spectra as a function of temperature indicate that the same conformation remains dominant in the melt, in a mesophase, and in the crystal at 150 K, with temperature-dependent conformational interconversion dynamics observed.

The three conformers lowest in energy (see Table 9) have C_1, C_S, and D_4 symmetry and were chosen from previous work[54] for comparison with the observed INS spectrum. These conformers can be described as rectangles [2334], [2343], and [3333], respectively, in which the digit indicates the number of C−C bonds between corner atoms. This notation originated for carbon atoms arranged on a diamond lattice[55] but is useful for approximating cases as well. The dihedral angles that make up the D_4 conformer match those found in the crystal. The calculated and observed spectra are presented in Figure 5. The number of peaks in the experimental spectrum suggests that the sample is conformationally pure. In the frequency range of 300−600 cm^{-1}, the D_4 conformer shows the most obvious agreement with experiment. The C_1 and C_S conformations show serious discrepancies, demonstrating again the sensitivity of the spectral features to conformational changes. The results of a linear fit of the calculated conformer frequencies to the observed frequencies are displayed in Table 10. The relative χ^2 value of each conformer indicates that the D_4 conformer is the one most likely present in the experimental spectrum. We can therefore conclude that vibrational and theoretical predictions are again in close agreement with X-ray crystallographic data and that the phase transition appears to preserve the molecular conformation.

Cyclotetradecane. Conformers EMS1 (C_{2h}), EMS2 (C_1), EMS3 (D_2), and EMD5 (C_1) of cyclotetradecane were among those selected for analysis from previous work[20] with the nomenclature retained. EMS1 and EMS2 can be described as rectangular conformations [3434] and [3344] in which the digits indicate the number of C−C bonds between the corner atoms on a diamond lattice.[55] The optimized geometries are consistent with the reference geometries[20] with a notable deviation observed in EMD5 in which one dihedral angle expected to be planar optimizes to −100°. Experimental and computed INS spectra are shown in Figure 6. EMS1 shows the best agreement with the observed spectrum, especially in the 300−600 cm^{-1} region. The number of peaks in the experimental spectrum also suggests that the sample is conformationally homogeneous within our detection limits. The calculated frequencies of each conformer are compared with the observed frequencies in a linear fit with the intercept forced to zero. The χ^2 values of each fit are compared and listed in Table 11. The calculated frequencies for the EMS1 (C_{2h}) conformer agree significantly better with the experiment than the other conformers with relative χ^2 values large enough to determine the presence of the EMS1 conformer with 95% confidence.

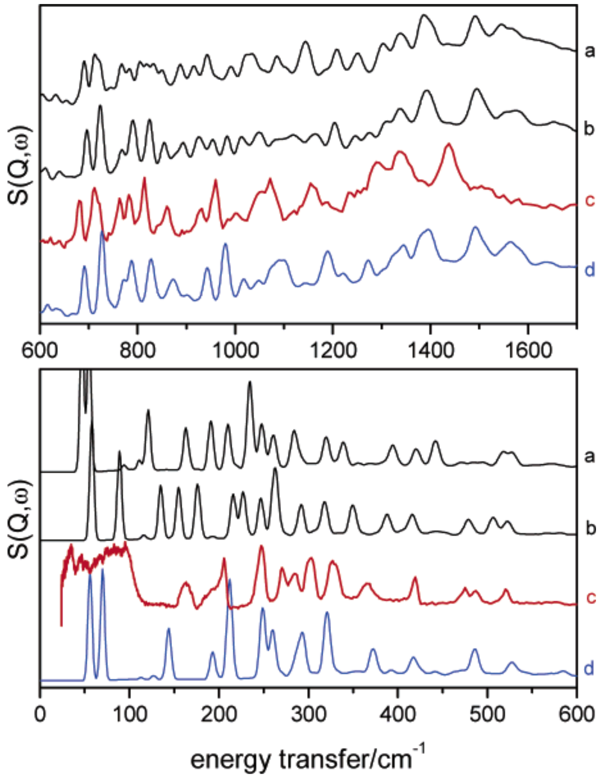

Figure 5. C3 (a), C2 (b), and C1 (d, blue) cyclododecane spectra, calculated with B3LYP/6-311G(d,p) and simulated using aClimax, compared with the experimental cyclododecane spectrum (c, red). The spectra displayed in the higher frequency range are magnified by a factor of 3 relative to those in the low-frequency panel.

TABLE 11: Results of Calculated and Observed Cyclotetradecane Frequencies Fit to a Linear Function with the Intercept Forced to Zero: $y = P1x$[a]

cyclotetradecane	$P1$	$P1$ error	χ^2	relative χ^2
EMS1 (C_{2h})	0.984	0.001	130	1.0
EMS2 (C_1)	0.982	0.002	275	2.1
EMS3 (D_2)	0.984	0.002	403	3.1
EMD5 (C_1)	0.988	0.002	373	2.9

[a] For this set of spectra, $j = 91$ with $F(60,60) = 1.5$ required to determine the presence of one conformer over another.

The crystal structure of cyclotetradecane at 116 K is triclinic in space group $P1$ with one molecule per unit cell.[56] The crystal consists of a single conformation having the same sequence of dihedral angles as the EMS1 (C_{2h}) conformer. We can therefore conclude from the vibrational data that the C_{2h} conformer is the dominant species, in agreement with the diffraction studies. This is the conformation predicted to be lowest in energy in this (see Table 12) and previous studies.[55] Solid-state ^{2}H NMR[25] and the ^{13}C NMR[24] spectra have been obtained over a temperature range that includes the melt, a mesophase, and the crystal at 175 K. These studies conclude that the same conformation persists through these phase transitions with dynamics observed due to temperature-dependent conformational reorientation. This

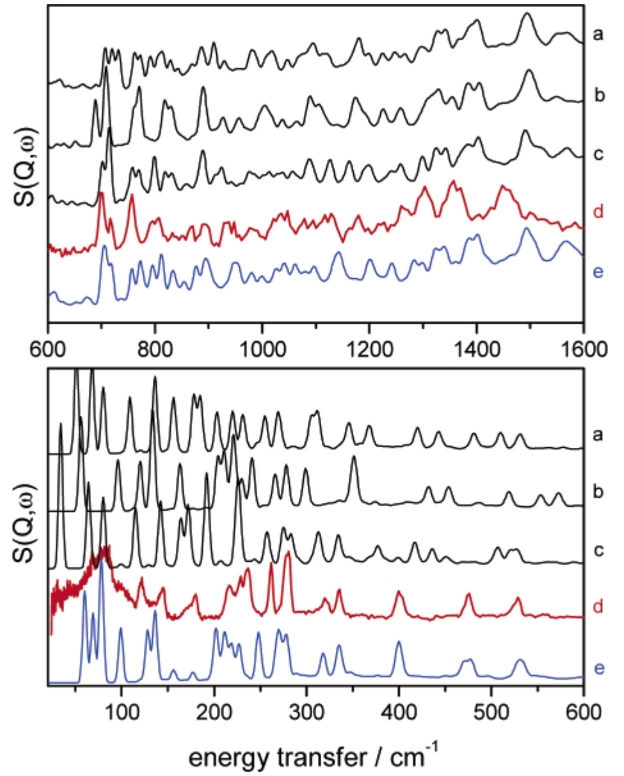

Figure 6. EMD5 (a), EMS3 (b), EMS2 (c), and EMS1 (e, blue) cyclotetradecane spectra, calculated with B3LYP/6-311G(d,p) and simulated using aClimax, compared with the experimental cyclotetradecane spectrum (d, red). The spectra displayed in the higher frequency range are magnified by a factor of 3 relative to those in the low-frequency panel.

TABLE 12: Relative Calculated Energies (kcal/mol) for the Conformations of Cyclotetradecane

cyclotetradecane	MM2[20]	B3LYP/6-311G(d,p)[a]
EMS1	0.0	0.0
EMS2	1.1	0.7
EMS3	1.5	2.8
EMD5	1.4	2.0

[a] This study.

does not preclude the presence of higher energy conformers, but it does indicate that their concentrations are negligible.

Conclusions

Several notable general differences exist between the theoretical and experimental spectra. The normal mode calculations consistently overestimate the experimental frequencies due to either inadequacy of the method, lattice forces, or anharmonicity in the vibrations. These hypotheses can be tested with solid-state vibrations or anharmonic corrections, but the computational cost is too large for the present study. Further, the nature of these deviations is very similar to that observed for other hydrocarbons for which it was found that inclusion of the intermolecular forces by use of a periodic DFT method resulted in a much improved agreement.[6,29]

Although the observed spectra indicate the presence of only one conformation, there is a possibility that there are many different conformations present in the low-temperature solid-state sample. Although the energy difference between isolated cyclohexane conformations is greater than that gained by crystallization,[41] higher energy conformers are more likely to be stabilized with crystallization as molecular size increases. Cyclododecane has an enthalpy of sublimation of 18 kcal/mol[57] and that found for cyclotetradecane[58] is 21 kcal/mol, yet the next most stable isolated conformations are only a few kcal/mol more energetic than those calculated to be the most stable. Thus, 10 or 20% enhancement of the packing energy by some suitable rearrangement might well result in a crystal that is more stable with a conformation that is not the lowest energy conformation in the isolated molecule. The cooling of these samples from room temperature to roughly 30 K took place over the course of several hours, yet was not controlled so high-energy conformations present at room temperature could be trapped in local minima. The observed spectra exhibit limited sensitivity: a conformation present in an amount of 5% or less is not likely to be detected using INS spectroscopy. The samples therefore appear conformationally homogeneous to within the limits of the data collection statistics and the resolution of the instrument.

The calculated conformers that are in closest agreement with experiment are also the conformers predicted by DFT and ab initio calculations to be the most energetically stable conformations in the gas phase. Furthermore, these INS spectra show conformational agreement with the cases in which the molecular conformation is known from X-ray crystal structure data. It seems that INS can be considered a viable method for determining the dominant molecular conformation present in a given crystal. Only the vibrational frequencies were quantitatively analyzed in this study, providing statistically significant results as to which molecular conformation is present in the experimental sample. If necessary in future studies, analysis of the calculated and observed relative intensities could be used quantitatively to determine the dominant conformation present in a given sample. In practice, the intensities are used in the present study to establish the correspondence between the calculated and observed features. The success of this method is largely dependent on the quality of the calculations. The advantage of the cycloalkanes in this type of study is that the intermolecular interactions are sufficiently weak that isolated molecule calculations provide a good representation of the molecule in the solid state. In studies to be published elsewhere, we have extended this method to biphenyl and the stilbene isomers where somewhat stronger intermolecular forces result in a molecular conformation in the crystal that is not a minimum in the isolated molecule potential surface.

This method of analysis is applicable only to the crystalline solid state. If molecular conformation in the solid state is of interest, then this method is useful if, for whatever reason, it is not possible to obtain, or to refine, diffraction data for the material of interest. Under those circumstances, this method may be one of the few methods that yields conformational information. The major limitation to the widespread utilization of this method is the need to obtain an INS spectrum at an appropriate facility. This will become much easier over the next few years as the Spallation Neutron Source becomes operational at Oak Ridge National Laboratory and the VISION spectrometer (http://materials.chem.utk.edu/vision.html) becomes operational. Due to design improvements, advances in neutron technology, and the enhanced flux of the SNS, VISION will be able to obtain spectra in 5 min that currently take 5 h to obtain.

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Supporting Information Available: Complete Reference 28. This material is available free of charge via the Internet at http://pubs.acs.org.

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