

Ab Initio and improved empirical potentials for the calculation of the anharmonic vibrational states and intramolecular mode coupling of N-methylacetamide

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ABSTRACT

The second-order Möller-Plesset *ab initio* electronic structure method is used to compute points for the anharmonic mode-coupled potential energy surface of *N*-methylacetamide (NMA) in the *trans_{ct}* configuration, including all degrees of freedom. The vibrational states and the spectroscopy are directly computed from this potential surface using the Correlated Corrected Vibrational Self-Consistent Field (CC-VSCF) method. The results are compared with CC-VSCF calculations using both the standard and improved empirical Amber-like force fields and available low temperature experimental matrix data. Analysis of our calculated spectroscopic results show that: (1). The excellent agreement between the *ab initio* CC-VSCF calculated frequencies and the experimental data suggest that the derived anharmonic potentials for *N*-methylacetamide are of a very high quality. (2). For most transitions, the vibrational frequencies obtained from the *ab initio* CC-VSCF method are superior to those obtained using the empirical CC-VSCF methods, when compared with experimental data. However, the improved empirical force field do yield better agreement to the experimental frequencies as compared with a standard AMBER-type force field. (3) The empirical force field in particular overestimates anharmonic couplings for the amide II mode, some of the methyl asymmetric bending modes, some of the out-of-plane methyl bending mode, and the methyl distortions. (4) Disagreement between the *ab initio* and empirical anharmonic couplings is greater than the disagreement between the frequencies. (5) However both the empirical and *ab initio* CC-VSCF calculations predict a negligible anharmonic coupling between the amide I and other internal modes. The implications of this is that the intramolecular energy flow between the amide I and the other intermolecular modes may be smaller than anticipated. These results may have important implications for the anharmonic force fields of peptides, for which *N*-methylacetamide is a model.

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1 Introduction

There is long standing interest in the spectroscopy and dynamics of *N*-methylacetamide (NMA). This is due in part because NMA acts as a simplistic model for the amide bond in peptides and proteins. Notwithstanding the deep and detailed experimental[1]–[10] and theoretical[11]–[18] investigations of NMA, relatively little is still known about the intramolecular coupling between different vibrational modes. In general, the effect of mode coupling on the vibrational spectrum will be to shift the harmonic frequencies either to the blue (more stiff) or red (more relaxed). In previous *ab initio* theoretical calculations of the energetics and harmonic vibrational spectra of *N*-methylacetamide, it was illustrated that one needs to scale the harmonic frequencies to reasonably compare with the experimental data.[12] In addition, the different conformations of NMA (*cis* and *trans*) require slightly different scaling factors. Furthermore, when the amide group is hydrogen bonded to water, this also requires rescaling of the force constants.[12] Thus, although the *ab initio* theoretical calculations of *N*-methylacetamide were of a reasonable level, the harmonic vibrational frequencies obtained required scaling in order to compare well with known experimental data.[12]–[14], [17], [18]

When the potential is available in an analytical form, one can perform a Vibrational Self-Consistent Field (VSCF) calculation in order to determine the frequencies and relative degree of mode coupling in the system. This has proven to be quite accurate and useful for a wide variety of problems such as (*Ar*)₁₃ clusters,[19] peptide-water complexes,[20] glucose,[21] and BPTI with almost 200 hydration waters.[22] Moreover, by extending the VSCF method using perturbation-corrections treatments, Jung and Gerber were able to deal quite successfully with the highly anharmonic coupled mode system, (*H*₂*O*)_{*n*}, *n* ≤ 8.[19] However, this method is as successful as the underlying analytical force field is accurate.

Recently, Chaban *et. al* have developed an *ab initio* vibrational self-consistent field method and illustrated that direct calculation of the anharmonic vibrational spectroscopy from an *ab initio* potential energy surface was feasible for molecules of up to 15 atoms or more. Furthermore, the *ab initio* VSCF method does not re-

quire a fitting of an analytic potential function, nor high order derivatives or scaling factors, in order to calculate anharmonic, mode coupled vibrational frequencies. This method, as well as a correlation-corrected extension to the *ab initio* VSCF method (CC-VSCF), was successfully applied to the calculation of the fundamental vibrational excitations of systems including: $(H_2O)_n$, $Cl^-(H_2O)_n$, $H^+(H_2O)_n$, $n = 1, 2, 3$, $H_2O - CH_3OH$ and glycine-water complexes with good results.[23], [24], [30]

It is our aim to apply this method for the calculation of the anharmonic vibrational spectrum of *trans N*-methylacetamide. In particular, we shall investigate the intramolecular mode coupling between different pairs of vibrational modes, as compared with results obtained from a calculation of the anharmonic vibrational spectrum using an empirical force field. We shall be able to directly assign a coupling strength to each pair of modes. This work represents a continuing investigation into the nature of anharmonic coupling in biological molecules.

2 Vibrational Self Consistent Field Method (VSCF) and Correlation-Corrected VSCF

If one begins with the mass-weighted vibrational Schrödinger equation and makes the separable Hartree approximation, then this leads to N single normal mode, Q_k , equations of the following form:[25]–[28]

$$\left[-\frac{\hbar^2}{2} \frac{\partial^2}{\partial Q_k^2} + V_k^n(Q_k) - \varepsilon_k^n\right] \psi_k^n(Q_k) = 0 \quad (1)$$

The effective potential for mode k , $V_k^n(Q_k)$ is given as the integral of the total potential over all other modes $l \neq k$ (equation 2). Equation 1 is solved self-consistently for each ε_k^n and the VSCF expression for the total energy of vibrational state n is thus a sum of all the individual mode energies minus a term which accounts for the double counting of the modes is:

$$E_{total}^n = \sum_{k=1}^N \varepsilon_k^n - (N-1) \left\langle \prod_{k=1}^N \psi_k^n | V(Q_1, \dots, Q_N) | \prod_{k=1}^N \psi_k^n \right\rangle$$

In order to account for correlation effects between modes, an effective perturbation treatment analogous to Möller-Plesset method (MP2) for electronic structure calculations, was employed. The theory behind the VSCF and correlation-corrected VSCF (CC-VSCF) approximation can be found in references 23-30.

The VSCF and CC-VSCF methods have been used in the calculation of anharmonic vibrational frequencies as well as mode-mode coupling for peptide-water complexes,[20] glucose,[21] BPTI with almost 200 hydration waters,[22] $(Ar)_{13}$ clusters,[29] and for $(H_2O)_n$, n up to 8 clusters.[19] Recently, the *ab initio* CC-VSCF method was also applied for the calculation of *ab initio* anharmonic vibrational states for $(H_2O)_n$, $Cl^-(H_2O)_n$, $H^+(H_2O)_n$, $n = 1, 2, 3$, $H_2O - CH_3OH$, glycine and a glycine-water complex.[23], [24], [30]

In the present study of the anharmonic vibrational spectroscopy of *N*-methylacetamide, we utilized an empirical potential, $V(Q)$, which is based on an Amber type of force field. Amber is one of the more widely used force fields in many biological studies.[31], [32] The effective potential for any mode k , $V_k(Q_k)$, can be derived from an expansion (Taylor Series) up to fourth order about a local/global minimum, and integrating over all modes $l \neq k$, with the following form:

$$\begin{aligned} V_k(Q_k) &= \frac{1}{2} \frac{\partial^2 V}{\partial Q_k^2} Q_k^2 + \frac{1}{6} \frac{\partial^3 V}{\partial Q_k^3} Q_k^3 + \frac{1}{24} \frac{\partial^4 V}{\partial Q_k^4} Q_k^4 + \\ &\frac{1}{2} \sum_{l \neq k}^N \frac{\partial^3 V}{\partial Q_k^2 \partial Q_l} Q_k^2 \langle \psi_l(Q_l) | Q_l | \psi_l(Q_l) \rangle + \\ &\frac{1}{2} \sum_{l \neq k}^N \frac{\partial^3 V}{\partial Q_k \partial Q_l^2} Q_k \langle \psi_l(Q_l) | Q_l^2 | \psi_l(Q_l) \rangle + \\ &\frac{1}{4} \sum_{l \neq k}^N \frac{\partial^4 V}{\partial Q_k^2 \partial Q_l^2} Q_k^2 \langle \psi_l(Q_l) | Q_l^2 | \psi_l(Q_l) \rangle \end{aligned} \quad (2)$$

The calculation of the effective potential, equation 3, in an *ab initio* method will scale unfavorably if one were to apply a Taylor Series expansion about a given configuration. Therefore the approach taken was to assume that the potential function can be well represented by including interactions between only pairs of modes, and calculating the potential on a two-dimensional grid.[19], [29] Our experience with this approximation, which neglects direct coupling between triplets of normal modes, has been very encouraging.[23], [24], [30] Thus in the *ab initio* method, the effective potential becomes:

$$V_{VSCF}(Q_1, \dots, Q_N) = \sum_{j=1}^N V_j(Q_j) + \sum_{i < j} V_{ij}(Q_i, Q_j) \quad (3)$$

Here $V_j(Q_j)$ is the diagonal term and $V_{ij}(Q_i, Q_j)$ are the pair-wise off-diagonal coupling elements. An electronic structure calculation is first used to calculate the equilibrium configuration. Then from diagonalization of the Hessian at this configuration, the normal mode coordinates are obtained. In order to calculate the potential at each normal mode point, a transformation back to Cartesian coordinates is made, and the potential energy is then calculated at this displaced geometry. The diagonal and mode-coupled potentials of equation III.4 were calculated on a 8-point and 8X8 grid which were later interpolated to a 16-point and 16X16 grid.

In order to investigate further the degree of anharmonicity in the amide modes, we have defined a scalar quantity, the *coupling strength* (CS), which will indicate the degree of mode-to-mode-coupling. Here the coupling strength (CS) is defined as:

$$CS_{ij} = (0.5) * \frac{(\langle \Psi_i^0(Q_i) \Psi_j^1(Q_j) | V_{ij} | \Psi_i^1(Q_i) \Psi_j^0(Q_j) \rangle + (\langle \Psi_i^1(Q_i) \Psi_j^0(Q_j) | V_{ij} | \Psi_i^0(Q_i) \Psi_j^1(Q_j) \rangle))}{(\hbar(\nu_j^0 - \nu_i^0))} \quad (4)$$

In equation 4 Ψ_i^0 and Ψ_i^1 represent the ground and first excited state wavefunctions for mode i . The wavefunctions are determined self-consistently using equation 1. In equation 4, V_{ij} is the coupling potential, defined by equation 3 (*ab initio*) and the off-diagonal terms of equation 2 (empirical).

3 Conclusions

In this work we address the issue of comparing anharmonic vibrational spectroscopy using two different methods for calculating the coupling between intramolecular vibrational modes. The anharmonic vibrational states and frequencies of *N*-methylacetamide were obtained for three potentials; a standard AMBER force field, an improved force field calculated to agree with existing experiments on this system, and a new *ab initio* anharmonic potential surface. For each of these potentials the first step involved computing the equilibrium structure. The starting structure was found from a simulated annealing simulation of the isolated *N*-methylacetamide using our modified empirical force field. The resulting low energy structure (*trans-NMA_{ct}*) was further minimized using a steepest descents method until the norm of the forces were ≤ 0.0001 . Other conformers of *NMA* were found by an adiabatic mapping of the rotation of the CO and NH methyl groups. Due

to the length of time required to calculate the *ab initio* VSCF potential energy surfaces, we have only calculated the anharmonic vibrational frequencies for the *trans-NMA_{ct}* configuration

We find that overall the comparison between the empirical, *ab initio* and experimental frequencies is good. In general, however; the *ab initio* CC-VSCF method illustrates a significantly better agreement compared with the experimental data. This particularly true for the amide I, II and III modes of *NMA*. In fact, most of the *ab initio* CC-VSCF modes are within 30 cm^{-1} of the experimental data. This is not the case for either the *ab initio* harmonic or empirical CC-VSCF calculations. In the case of the empirical VSCF frequencies, the amide I, amide II, and amide III modes at 1678, 1596 and 1217 cm^{-1} are significantly shifted from the anharmonic CC-VSCF *ab initio* (1751, 1547 and 1283 cm^{-1}) and experimental frequencies (1708, 1511 and 1265 cm^{-1}). This could indicate an overestimation of the intramolecular coupling potential for these modes. In order to understand how different modes are coupled together, we defined a scalar quantity, the coupling strength. This coupling strength is related to the probability of two modes transferring vibrational energy. By calculating the intramolecular coupling strength for both the *ab initio* and empirical force fields, we find a few surprising results. Firstly, the amide I mode does not appear to couple to other internal vibrational modes. This is in contradiction to the results of Hamm and co-workers, which suggest that an intrinsic property of the amide I mode is to very quickly (450 fs) transfer vibrational energy to other internal modes.[33] We also find that the coupling of the amide II mode to other internal modes is overestimated in the empirical force field. This could in fact led to the calculation of intramolecular energy redistribution (IVR) pathways which are incorrect. Therefore, a comparison between the coupling strength calculated with the empirical and *ab initio* force fields is a first step at not only benchmarking empirical potentials, but also at later empirical force field refinement.

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