QUANTUM CHEMISTRY SIMULATIONS OF VIBRATIONAL SPECTROSCOPY TO DETERMINE THE STRUCTURE OF TROPINE

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BACKGROUND

One modern route to determining the structure of biomolecules is vibrational spectroscopy, where the molecule of interest is irradiated by infrared light and vibrates at characteristic frequencies. However, many molecules exhibit several low-energy structures, called "conformers", even at biologically relevant temperatures. In this scenario, each conformer's unique spectral signatures can appear simultaneously, which further complicates the problem for experimentalists since these spectral responses cannot be readily disentangled without knowing the spectrum of each individual conformer. Quantum chemistry computations can disentangle these results since conformer-specific vibrational spectra can be calculated and directly associated with a particular structure. The protonated and neutral forms of tropine, a synthetic precursor to molecules that share the same nitrogenous bicyclic structure, including homatropine and cocaine, are the primary focus of this project. An experimental vibrational spectrum of tropine is not yet available (although our collaborators at EPFL in Switzerland have agreed to generate them upon completion of this project). However, an experimental spectrum for the related protonated homatropine ion has been obtained through recently developed—and conformer-specific—IR-IR-UV hole-burning from the same collaborator. The anticipated outcome of this study for tropine is an isolation of the structure-specific spectral signatures of the tropine ring system that is common to many of these pharmacologically relevant compounds.

RESEARCH APPROACH

Structural Search & Relative Energies – Molecular vibrations involve stretching chemical bonds, which are inherently quantum mechanical in nature. To simulate such systems properly, computer simulations based solely on the underlying principles of quantum mechanics are used in this study. Using an automated search procedure (devised for this project), optimized structures and relative energies were generated for all possible stable structures. Harmonic frequencies were then computed for these structures. These results allow for thermally-weighted spectra to be produced, based on conformer populations that predict the experimental spectrum.

Simulating Vibrational Spectra – For quantitative congruence with experimental spectra, relaxing this harmonic approximation—to include anharmonic and mode-coupling effects—is required. This requirement has motivated the use of more computationally demanding methods, including *ab initio* molecular dynamics (AIMD) and eigenstate-based methods. AIMD calculations allow the molecule to "wiggle" through real-time dynamics. Dynamical observables can be recorded at each timestep, including the dipole moment of the molecule. By computing the correlation, α, of this dipole moment over time (Equation 1) and its Fourier transform, a vibrational spectrum can be obtained.

$$\alpha(\Delta) = \langle \vec{\mu}(t + \Delta) \cdot \vec{\mu}(t) \rangle \qquad (1)$$

Eigenstate-based approaches, such as the mean-field vibrational SCF method, obtain vibrational wavefunctions and energies by solving the time-independent Schrödinger Equation.

RESULTS AND CONTRIBUTIONS TO-DATE

The conformer search for neutral and protonated tropine yielded 13 and 11 unique structures, respectively (Figure 1). From these structures, we determined unique spectral signatures that distinguish the low-energy conformer from its energetic neighbors. In particular, a bright N-H stretch in the lowest-energy conformer of protonated tropine is red-shifted by ~200 cm^{-1} due a hydrogen bond between the excess proton and the terminal O-H unit. This type of analysis provides insight to our experimental collaborators, as this signature is distinguishable from other conformers in a thermally-weighted spectrum (Figure 2).
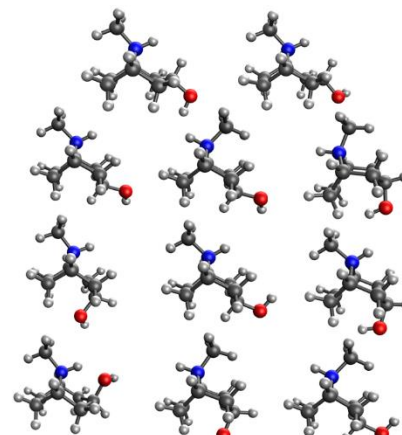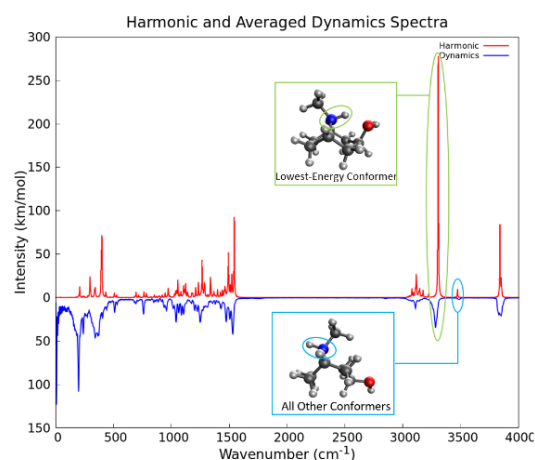

Figure 1: Structural Flexibility of TropineH+

Figure 2: Thermally-weighted Harmonic and AIMD Spectra at 298K

Despite claims to the contrary in the literature,[2] our own AIMD simulations (on this molecule and others) have demonstrated that dynamics-generated spectra were surprisingly similar to nominally more approximate harmonic spectra (Figure 2). Therefore, these simulations provided little additional insight.

Instead, we turned to eigenstate-based approaches, which offer a systematically improvable route to generate quantitatively correct vibrational spectra. These established methods are commonly used for these anharmonic simulations. While using such techniques for the entire spectrum, however, we encountered some common challenges that arise in the simulation of biomolecules. In particular, strongly coupled high and low-frequency modes yielded unphysical solutions. It is not uncommon for existing literature to simply exclude these modes or scale down the coupling. Therefore, much of our recent effort has been devoted to retooling some of the widely used methods for spectroscopy simulations.

After considerable investigation using smaller test cases, the problem was isolated to one of the more egregious approximations in these simulations, which is the limitation of the vibrational coupling to a fixed order—in this case, pairwise mode coupling—in the expansion of the full 72-dimensional vibrational potential for my system. However, increasing dimensionality of the potential representation is no small feat. In fact, stepping up from pairwise to 3-mode coupling for tropine is nearly intractable. This situation motivates the development of new methodology to reduce the computational cost of obtaining higher dimensional, and therefore more accurate potential energy scans for modestly-sized molecules to handle problematic vibrations. Addressing these issues is necessary to move forward, but the outcome will be both a final determination of spectra for these complexes, as well as new methodology.