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Calculation of the Vibrational Stark Effect Using a First-Principles QM/MM Approach

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Abstract

The proper description of the electric environment of condensed phases is a critical challenge for force field methods. To test and validate the ability of the CHARMM additive force field to describe the electric environment in aqueous solution combined QM/MM calculations have been used to calculate the vibrational Stark effect (VSE). We utilized a first principles methodology using correlated electronic structure techniques to compute the Stark shift between the gas phase and solvent environments and between two different solvent environments of three VSE probes containing acetonitrile or fluorine functionalities which have been well-characterized experimentally. Reasonable agreement with the experimentally determined Stark shifts is obtained when the MM atoms are described by the CHARMM additive force field, though it is essential to employ an anharmonic correction in the frequency calculation. In addition, the electric field created by the solvent is computed along the CN bond and a theoretical Stark tuning rate is determined for acetonitrile and shown to be in satisfactory agreement with experiment.

Keywords

Stark spectroscopy; QM/MM frequency calculations; force fields

The vibrational Stark effect (VSE) refers to the characteristic shift of a specific vibrational frequency in response to an electric field.^{1,2} Measurement of the Stark tuning rate, $|\Delta\mu|$, which quantifies the change in the vibration in different environments, is an effective method to monitor the electrical environment of a probe molecule. The observed change in frequency is given by the equation

$$hc\Delta\nu = -\Delta\mu \cdot F_{\text{ext}}$$

where the Stark tuning rate can be expressed in units of $\text{cm}^{-1}/\text{MV}/\text{cm}$ to easily compute the linear shift in frequency with applied field. This shift originates from changes in the vibrational dipole moment, and the macroscopic response was originally described by Liptay.³

Stark effect probes for use in biochemical studies should possess a characteristic frequency in an otherwise uncongested region of the IR spectrum and be sensitive to small changes in the electrical environment. Groundbreaking work by Boxer and co-workers have measured Stark tuning rates for a variety of nitrile probes,^{4,5} created nitrile probes in proteins by conversion of cysteine thiols to thiocyanates,⁶ and used a nitrile containing probe to monitor

changes in the enzyme active site of human aldose reductase,⁷ Lockhard and Kim measured the electric field at the interface of an alpha helix in water by covalently attaching a probe to the helix.⁸ Additional work has measured the Stark shift between two different solvent environments for various nitrile probes both experimentally^{9,10} and theoretically.^{11–13} The work of Getahun et al.⁹ measured the Stark shift of acetonitrile and several other simple nitrile probes between water and tetrahydrofuran (THF) and found that water had a blueshift (higher frequency) of 8.3 cm^{-1} , relative to THF. Lindquist and Corcelli used a PM3 QM/MM theoretical methodology specially parametrized for VSE to calculate the anharmonic frequencies and IR line shapes for Stark effect probes in different environments and used this methodology to calculate the Stark shift of acetonitrile from THF to water^{11,13}, and found the Stark shift to be 6.3 cm^{-1} .

In this work, we use combined quantum mechanical/molecular mechanical (QM/MM) calculations to calculate the vibrational frequency of several well-characterized VSE probes in the gas phase and in solvent environments using the ab initio QM method in combination with the CHARMM additive force field. This first principles approach is developed with the goal of using VSE calculations of nitrile probes to better understand the electrostatic environment in macromolecules and provide a basis for assessing how these environmental effects can be properly represented in computational models.

The focus of this study was computing vibrational Stark shifts due to changes in the environment rather than on changes induced by applying external electric fields as is typically performed in VSE experiments. This type of shift might be characterized as a solvochromatic shift, rather than a Stark shift, since the shift is caused by hydrogen bonding and specific interactions with the solvent and thus is dependent on the local solvent structure around the probe molecule.¹⁴ However, it was noted solvochromism and electrochromism (the Stark shift) have the same fundamental cause,^{3,14} and we use the term Stark shift in the present paper as our methodology is calculating the impact of the electric field of the solvent on the vibration of the probe molecule. Several experimental studies from Boxer and coworkers have focused on the VSE and measured Stark tuning under an applied electrical field to quantify the Stark tuning rate for a variety of probe molecules.^{4,6,15,16} While these experiments yield valuable information, the focus on electric field means that experimental data is often only available for a given Stark probe in one solvent. Such experimental data can be used as our benchmark data if an experimental measurement of the vibrational spectrum in the gas phase is also available. Gas phase vibrational spectra have been collected for acetonitrile¹⁷ and fluorobenzene¹⁸ and will be used as the benchmarks to compute the gas phase to solvent shift.

The gas phase frequency was determined for each probe molecule with MP2 and the 6-31G* basis set, first enforcing the harmonic approximation and then including an anharmonic correction using vibrational perturbation theory, VPT2.¹⁹ To determine the frequency in the solvent environment, for each of the 200 probe/solvent configurations collected from the MD simulations, an MP2 optimization of the probe molecule, followed by an MP2 frequency computation, was performed in the electric field created by the MM solvent molecules. Effectively, a set of point charges that represent the MM atoms is added in the MP2 computation to capture the electrostatic environment created by the solvent. Again, the frequency is computed both with and without the anharmonic correction, and the average frequency over the 200 configurations is determined. Experimental frequency data for acetonitrile in water and tetrahydrofuran (THF) are available⁹, while experimental data for fluorobenzene is available in methyl-tetrahydrofuran (mTHF).¹⁶

The Stark shifts between the solvent and gas phases for each probe molecule are summarized in Table 1. In all cases, the agreement with experiment is rather poor when the

harmonic approximation is used. In the case of acetonitrile in water the computed shift is even in the wrong direction. Significant improvement is gained when the anharmonic correction is included with VPT2, and the computed Stark shift between the gas phase and solvent environments is in good agreement with the experimental benchmarks. Instead of the VPT2 approach, anharmonic effects can also be included with transition-optimized shifted Hermite (TOSH) theory,²⁰ which has been purported to be more accurate than VPT2 in some cases. We investigated using this alternative and found that, while the TOSH frequencies were systematically lower by around 5 cm^{-1} , there was no difference in the computed Stark shifts.

For two model nitrile probes, acetonitrile and tolunitrile, experimental frequency data in two different solvents, water and THF, is available. THF is selected because its low dielectric constant (7.58) is assumed to approximate the average dielectric environment in the hydrophobic interior of a protein.⁹ Thus, the electrostatic environment shift between water and THF might be analogous to the change in the electric environment that would be experienced by a vibrational probe upon going from aqueous solution to a protein interior.

The frequency of the Stark probe vibration was computed in the same way described above, and the computed average frequencies and Stark shifts upon going from water to THF are given in Table 2. For acetonitrile in THF, the average frequency determined with this method is 2237.0 cm^{-1} , and in water is 2239.2 cm^{-1} , giving a Stark shift of 2.2 cm^{-1} when the harmonic approximation is used. When the anharmonic correction is employed, the average frequency in THF is 2199.1 cm^{-1} , and in water is 2202.7 cm^{-1} , giving a Stark shift of 3.6 cm^{-1} . The anharmonic correction in both solvents is relatively similar in magnitude but significantly larger than in the gas phase. The inclusion of the anharmonic correction gives a larger Stark shift that is in better agreement with the experimental benchmarks for the water/THF shift for acetonitrile.

For tolunitrile in THF, the average computed frequency is 2210.1 cm^{-1} ; in water it is 2213.1 cm^{-1} , giving a Stark shift of 3.0 cm^{-1} with the harmonic approximation. When the anharmonic correction is employed, the average frequency in THF is 2169.0 cm^{-1} and in water is 2173.1 cm^{-1} , giving a Stark shift of 4.1 cm^{-1} , in reasonable agreement with the experimental benchmark.

In the computations presented above, only the probe molecule was included in the QM region of the QM/MM computation. Since a hydrogen bond includes more complex interactions than simple electrostatics, we also examined the effect of including the nearest solvent molecule in the QM regions for the acetonitrile/water and acetonitrile/THF systems. Reimers and Hall report in their detailed analysis of the solvent structure of acetonitrile that “the solvation is controlled by a complex web of hydrophobic and hydrophilic interactions”²¹, thus including the directly interacting solvent molecule might provide additional insight into the Stark effect of these molecules. However, converging the intermolecular structure for small non-bonded complexes presents a significant computational challenge and even with conformational space restricted by the presence of the other solvent atoms in the MM region, not all the configurations could be optimized. However, for both solvents, approximately 25% of the configurations reached a converged minimum with no imaginary frequencies. To insure that these configurations were representative of all the configurations, the average frequency for just these configurations was compared to the average for all the configurations for the smaller QM region where all the cases were convergent. The average for the selected set of configurations was within 1 cm^{-1} of the average for all configurations, indicating that the subset is appropriately representative of the full set of configurations. The average frequencies and shifts for the calculations that include both acetonitrile and the nearest solvent molecule are shown in

Table 3. The Stark shift is significantly larger, 14.4 cm^{-1} , versus that for acetonitrile alone as the QM region (Table 2). To further investigate this result, we computed the electric field along the CN bond for each of configurations. The average field (RMS average since both positive and negative fields were computed) is also shown in Table 3, along with a calculated Stark tuning rate, computed by dividing the Stark shift by the change in the average field between the two solvents. The calculated Stark tuning rate is 0.35 MV/cm^{-1} , in reasonable agreement with the experimental value of 0.44 MV/cm^{-1} .^{4,16} It may be anticipated that the calculated Stark tuning rate would increase and the agreement would improve further if the anharmonic correction were employed in the frequency calculations as above.

Since the optimization of the probe/solvent cluster is extremely time consuming and can only be converged for about a fourth of the overall configurations, we investigated an alternate computational methodology to compute the Stark shift. In this method, the same solvent/probe configurations were used as the starting configuration for a 5 ps (1 ps equilibration and 4 ps production) QM/MM dynamics simulation, where the forces on the probe molecule were determined with MP2 at every timestep of the simulation. The velocity autocorrelation function is collected, and the Fourier transform of this function gives the calculated IR spectrum. The peak between 2000 and 3000 cm^{-1} is normalized and fit to a Lorentzian function to determine the position of the peak maximum, which is taken as the frequency of the nitrile moiety. For acetonitrile in THF, the average frequency determined with this method is 2245.0 cm^{-1} , and in water is 2264.1 cm^{-1} , giving a Stark shift of 19.1 cm^{-1} . (Table 3) Dividing this shift by the computed electric field calculated from the initial configurations gives a computed Stark tuning rate of 0.46 , in excellent agreement with experiment.

In the present letter the ability of a first principles QM/MM approach to calculate the vibrational Stark effect in the context of the CHARMM additive FF is shown. These results indicate that the methodology may be suitable for the study of vibrational shifts of probe moieties in more heterogeneous environments such as proteins and nucleic acids. The results also indicate the CHARMM additive force field to provide a satisfactory representation of condensed phases. Electrostatic parameters in the force field have been optimized to reproduce the behavior of condensed phases, and the results of these studies show that they provide a sufficiently accurate representation of the solvent environment that the Stark shift can be detected and the experimentally observed blueshift (higher frequency) of the probe molecules in water compared to THF correctly reproduced. The inclusion of the anharmonic correction to the QM frequency computation is essential to correctly predict the direction of the Stark shift between the gas phase and a solvent environment and also provides improved agreement with the experimental results. Further, we have also shown that the Stark tuning rate can be computed quite accurately if the QM region includes both the Stark probe and the nearest interacting solvent molecule or if a full QM/MM dynamics approach is utilized. This first-principles approach to computing Stark shifts should be equally applicable to all types of Stark probe molecules and does not require the optimization of any additional QM/MM parameters and should provide a general computational methodology for understanding Stark vibrational spectra.

Computational Details

Molecular dynamics simulations were performed with the CHARMM program^{22,23} using the CHARMM general force field.²⁴ For each solvent, a cubic solvent box approximately $28\text{ \AA}$ on each side was constructed and minimized with the steepest descent (SD) algorithm for 10,000 steps. A 2 ns molecular dynamics (MD) simulation at 298 K was then performed to equilibrate each solvent box. The probe molecules were minimized in the gas phase to a

gradient of 10^{-6} kcal/mol/Å and placed in the equilibrated solvent boxes. In all cases, solvent molecules within 2.0 Å of the probe molecule were removed to avoid direct contact with the probe. The box was again minimized with the SD algorithm for 5000 steps, and an additional 2 ps simulation was performed for equilibration, followed by a 20 ns production simulation. From these simulations, a snapshot was collected every 100 ps, yielding 200 solvent/probe configuration snapshots collected for the QM/MM analysis. All the QM/MM computations utilized the recently developed CHARMM/Q-Chem interface.^{25,26} The probe molecule and in specific cases, one solvent molecule, was designated as the QM region and the surrounding solvent molecules were the MM region. The QM region was treated with MP2 in conjunction with 6-31G* basis set. Additional details of the methods are presented in the supporting information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Computed gas phase to solvent Stark shifts using MP2 and the 6-31G* basis set.

acetonitrile (ACN)	water – gas phase	THF – gas phase
harmonic	1.4	–0.8
anharmonic	–9.2	–12.8
experiment	–7.6	–14.7
fluorobenzene (FLUB)	NA	mTHF – gas phase
harmonic		–1.4
anharmonic		–3.7
experiment		–5.8

All values given in cm^{-1} . The solvent environment was represented with the CHARMM additive force field. NA indicates that experimental data is not available.

Table 2

Frequency data and solvent Stark shifts for nitrile probes computed with MP2 and the 6-31G* basis set.

	gas phase	water	THF	water – THF
acetonitrile (ACN)				
harmonic	2237.8	2239.2 (0.26)	2237.1 (0.17)	2.2
anharmonic	2211.9	2202.7 (0.49)	2199.1 (0.47)	3.6
experiment	2267.7 ¹⁷	2260.1 ⁹	2251.8 ⁹	8.3
tolunitrile				
harmonic	2209.1	2213.1 (0.48)	2210.1 (0.10)	3.0
anharmonic	2179.1	2173.1	2169.0 (0.93)	4.1
experiment		2234.4 ⁹	2228.8 ⁹	5.6

All values given in cm^{-1} and standard error for computed values given in parenthesis. The solvent environment was represented with the CHARMM general force field.

Table 3

Frequencies, solvent Stark shifts, electric fields and Stark Tuning Rate for acetonitrile with the probe and the nearest solvent molecule considered in the QM region for the harmonic vibrational analysis and the probe considered the QM region for the QM/MM dynamics.

	water		THF		water – THF	
	Vib. Freq.	Electric Field	Vib. Freq.	Electric Field	Δ Vib. Freq.	Δ Electric Field
Harmonic	2248.4	69.75	2234	28.5	14.4	41.25
QM/MM dynamics	2264.1		2245		19.1	
Experimental	2260.1 ⁹	NA	2251.8 ⁹	NA	8.3	NA
						0.44, 4.16

Vibrational frequencies (Vib. Freq.) in cm^{-1} , electric field is the RMS average in MV and $\Delta\mu$ is the vibrational stark tuning rate ($\Delta\mu = \Delta\text{Vib. Freq.}/\Delta\text{Electric Field}$) in MV/cm^{-1} .