Successful Prediction of 1eV Stokes Shift from QMMM Application of Linear Response Theory[1]

Ross C. Walker[‡], Melanie de Souza[†], Ian P. Mercer[†], Ian R. Gould[‡] and David R. Klug[†]

*Molecular Dynamics Group[†] and Biophysics & Biological Chemistry Group[‡]
Department of Chemistry, Imperial College of Science, Technology & Medicine, London, UK.*

Abstract

The dynamics of the alcohol oxidation protein Liver Alcohol Dehydrogenase (LADH *Figure 1.*) have been studied using a methodology that couples classical molecular dynamics simulations with hybrid Quantum Mechanical / Molecular Mechanical (QMMM) calculations. Application of a methodology based on linear response theory and detailed balance developed by Mercer *et al.*[1] allows both theoretical steady-state and time-dependent data to be compared with experiment.

Previous work has shown that this composite quantum mechanical / molecular mechanical approach can recreate small relaxations in solvated molecular systems[1,2] allowing the prediction of optical absorption and emission spectra for direct comparison with experimental observables. It is demonstrated here that this exact same methodology also works for relaxations within a protein, even when the relaxation is as large as 1 eV giving very good agreement with experimental data (*Figure 2.*)
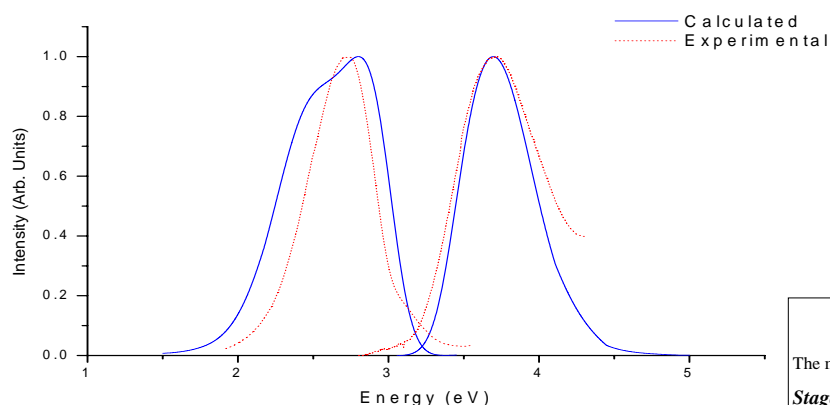
Figure 1. Cartoon representation of the crystal structure[3] of Horse Liver LADH (1LDY[3]) at 2.5 Å.

Figure 2. Comparison of average calculated (solid) and experimental (dotted) absorption and emission spectra for LADH.

Methodology

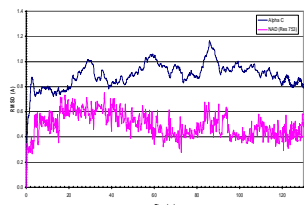The methodology used is summarised by the flow chart in *figure 3*.

Stage 1

Classical molecular dynamics is employed using the Amber force field[5] and AMBER suite[6] of molecular dynamics programs to obtain an equilibrated MD trajectory (*figure* 3a) of the LADH dimer at 300K. Snapshots of the structure are taken at 2fs intervals over a production run length of 10ps.

Stage 2

The MD trajectory snapshots are used to produce a set of 5,000 time ordered QM/MM input structures for the *ab initio* package Gaussian 98A7[7]. A single point CIS/3-21G* calculation is then performed on each structure with the NADH coenzyme forming the QM section with the point charges of the surrounding protein and solvent included in the one electron Hamiltonian. This yields a fluctuating energy gap (*figure 3b*).

Stage 3

From the fluctuating energy gap we can find, by using equation 1, the autocorrelation function of the energy gap fluctuations $M(t)$ (*figure 3c*). The spectrum of oscillators (*figure 3d*) is then found by taking the Fourier transform of this.

$$M(t) = \frac{1}{\Delta^2} \int_{-\infty}^{\infty} \delta\omega_{ab}(t+\tau)\,\delta\omega_{ab}(\tau)\,d\tau \qquad (1)$$

Stage 4

From the spectrum of oscillators we can, by assuming linear response, construct the optical absorption spectra. The emission spectrum is found by assuming that the excited state potential energy surface has the same profile as that of the ground state, but with the minimum shifted along the relaxation coordinate. In order to introduce a Stokes shift, $M(t)$, is modified to satisfy detailed balance, imparting a complex component. This makes the response of the system conform to the fluctuation-dissipation theorem[8]. Detailed balance is included by operating on the spectrum of oscillators $J(\omega)$, given by the Fourier transform of $M(t)$, so that positive frequencies are related to their negative counterparts by a Boltzman coefficient[9] such that

$$J(-\omega) = \exp(-\hbar\omega/kT)\,J(\omega) \qquad (2)$$

A modified semiclassical form of the spectral density is formed to satisfy this relationship which can then be back Fourier transformed to yield a modified form of $M(t)$ which imparts a complex component for the linear response function resulting in a Stokes shift between the calculated absorption and emission spectra.

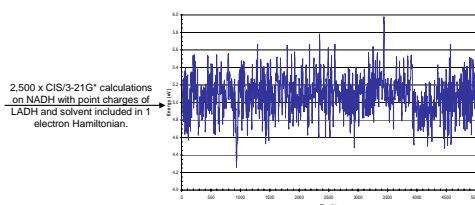**Figure 3a.** RMSD of Alpha carbons and NADH Residue 753 of LADH against time for molecular dynamics trajectory.

2,500 x CIS/3-21G* calculations on NADH with point charges of LADH and solvent included in 1 electron Hamiltonian.

Figure 3b. CIS energy gap vs time for LADH/NADH Res 753.

$$M(t) = \frac{1}{\Delta^2} \int_{-\infty}^{\infty} \delta\omega_{ab}(t+\tau)\,\delta\omega_{ab}(\tau)\,d\tau$$

Figure 3d. Spectrum of oscillators obtained by Fourier transforming *M(t)*.

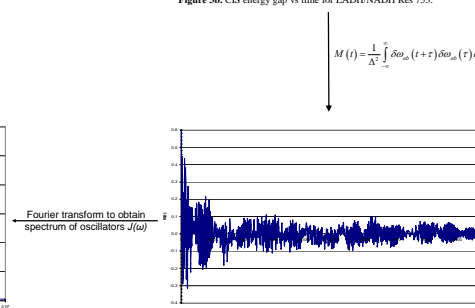Fourier transform to obtain spectrum of oscillators J(ω)

Figure 3c. Autocorrelation function M(t) of LADH/NADH Res 753 fluctuating energy gap.

Conclusions

We have:

· Shown that an *ab initio* QM/MM method is capable of reproducing the experimental optical absorption and emission spectra for NADH complexed with LADH in water.

· Found that through vibrations alone and employing just ground state equilibrium dynamics it is possible to accurately predict the existence of a Stokes shift between the absorption and emission spectrum as large as 1 eV.

· Shown that the theory of linear response and the associated approximations made still holds for systems where the reorganisation energy is very large.

· Found that good parameterisation of the NADH moiety is essential to obtaining accurate results and through this have found that the reorganisation upon optical excitation is largely independent of solute-solvent interactions and instead is due to internal vibrations and rotations within the nicotinamide moiety.
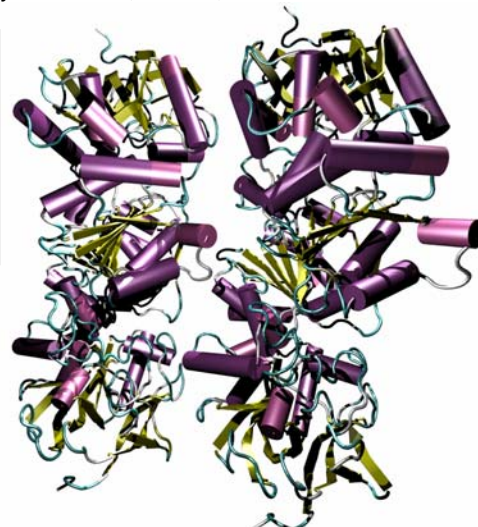
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