Successful Prediction of 1eV Stokes Shift from QMMM
Application of Linear Response Theory¹

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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 systems² 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 2. Comparison of average calculated (solid) and experimental (dotted) absorption and emission spectra for LADH.

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.

Figure 3a. RMSD (A)

Conclusions

Figure 3d. 0.0 0.4 0.6 0.8 1.2 1.4

Figure 3c. 0.000 0.005 0.030 0.060 0.090

Methodology

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

Stage 1

Classical molecular dynamics is employed using the Amber force field⁷ and AMBER suite⁸ 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 216 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 98A⁹. 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 (figure 3c).

\[ M(t) = \frac{1}{N} \sum_{\omega} \delta \omega \int_{-\infty}^{\infty} \delta \omega (t) \delta \omega (t + \tau) \exp (-\hbar \omega / kT) d\tau \]

(1)

Stage 4

From the spectrum of oscillators we can, by assuming linear response, construct the optical absorption spectrum. The emission spectrum is found by using 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, the excited state potential energy surface is varied by taking the Fourier transform of this.

\[ J(-\omega) = \exp (-\hbar \omega / kT) J(\omega) \]

(2)

A modified semiclassical form of the spectral density is formed to satisfy this relationship which may 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.

References