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Molecular Dynamics Simulations

An Ab Initio Microscope: Molecular Contributions to the Femtosecond Time-Dependent Fluorescence Shift of a Reichardt-Type Dye**

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Despite decades of effort, the properties of liquid water are not fully understood. In recent years it was found that geometric confinement has a strong effect on water, making it quite different from the bulk.[1] To understand protein functionality, agglomeration, and folding, as well as DNA stability, it appears to be essential to explicitly consider the presence of water.[2]

With current IR-based spectroscopic techniques, it is possible to monitor rapid photochemical reactions.[3] These techniques are, however, severely limited by strong absorption due to water, in addition to spectral crowding. To overcome these limitations, compounds with isotopically substituted carbonyl groups have been used.[4] IR spectroscopy observes the hydrogen-bond network indirectly by its coupling to the vibrational modes. Fluctuations of the hydrogen-bond network can be directly measured by THz spectroscopy which probes the dielectric bulk response.[5] Inside biomolecules or confinements, the absorption background of water can be entirely avoided when the fluorescence of a suitably placed chromophore is monitored. For this purpose, dyes are employed whose fluorescence depends strongly on solvent polarity.[6] In this context, the molecular probe *N*-methyl-6-oxyquinolinium betaine (MQ) is especially attractive because of its small size and water solubility, allowing insertion into DNA or proteins. Structurally, it resembles the polarity indicator dye introduced by Reichardt and coworkers.[7] The local THz spectrum, up to the far-IR intramolecular modes, can then be extracted almost quantitatively from the time-dependent Stokes shift (TDSS) of its fluorescence as measured by femtosecond spectroscopy. The connection between TDSS data of MQ and the THz spectrum of its surroundings has been established by simple dipolar continuum theory.[8] It should be noted that the Stokes shift of the chromophore represents only an indirect measurement of the water dynamics. In addition, the presence of the chromophore has the potential of affecting this very water dynamics to a certain extent.

However, the time-dependent dielectric response can be traced back to the structure and dynamics around the molecular probe in atomistic detail with the help of molecular dynamics simulations in combination with the experimentally observed evolution of the Stokes shift.

Published attempts at describing time-dependent solvation with molecular dynamics used either a quantum mechanics/molecular dynamics (QM/MM) approach, including only the solute and a few water molecules in a quantum mechanical treatment,[9] or a model potential derived from quantum mechanical calculations of the chromophore.[10] In our approach, we use density functional theory (DFT) for solute and solvent, which is known to yield an accurate picture of solvent effects and the dynamics of hydrogen-bond networks, also for excited-state solutes.[11] Instead of the dielectric linear response of the solvent or the time-dependent solvation energy, we compute the time-dependent fluorescence emission wavelength directly from nonequilibrium MD. This allows us to simulate the full TDSS experiment from first principles—without preadjusted parameters and assumptions about the solvent response, including full electronic polarization and all intramolecular degrees of freedom. We performed molecular dynamics simulations in the T_1 triplet state, providing an efficient approach for excited-state dynamics. In a previous paper we verified that the dipole moment and forces of the S_1 state of MQ are equally well described by both the T_1 state and time-dependent (TD-) DFT.[12] The Stokes shifts in turn were computed by TD-DFT in order to obtain more accurate excitation energies. For computational details see the Supporting Information.

MQ is formally a zwitterionic molecule with a large dipole moment (Figure 1). In agreement with previous static calculations the MD simulations performed here yield strong hydrogen bonds at the electron-rich MQ oxygen, which are weakened upon electronic excitation of the molecule.[12] The radial distribution functions show that the coordination number of 3 remains unaffected by this weakening (see the Supporting Information). When visually examining the trajectory, we find MQ to be inside a broad cavity in the solvent, generated by its hydrophobic planar π-system.

MQ shows a strong reduction of the molecular dipole moment upon electronic excitation (Figure 1). We previously computed this change of dipole moment to be from 10.2 D to 6.8 D in the gas phase.[12] In aqueous solution, we find a reduction from 22 D to 14 D (computed from Wannier centers, averaged over ten conformations in the corresponding relaxed trajectories.) As the large ground-state dipole moment induces a strong alignment of the solvent molecules

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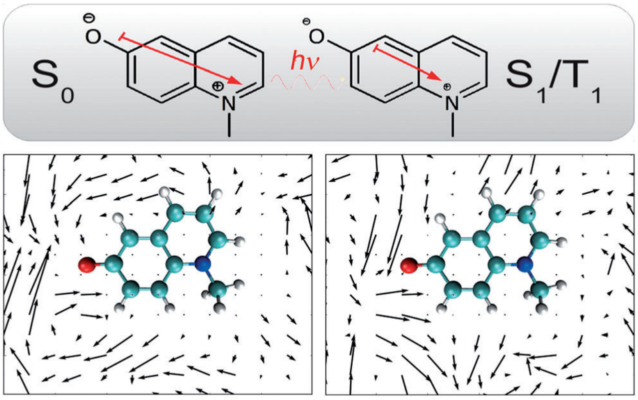

Figure 1. Schematic illustration of the change in the dipole moment upon electronic excitation of MQ (top, not to scale), averaged orientations of water molecules around solvated MQ in the ground (left) and in the excited state (right). The length of the arrows corresponds to a preferential orientation, obtained by ensemble averaging over the MD trajectory. For details see the Supporting Information.

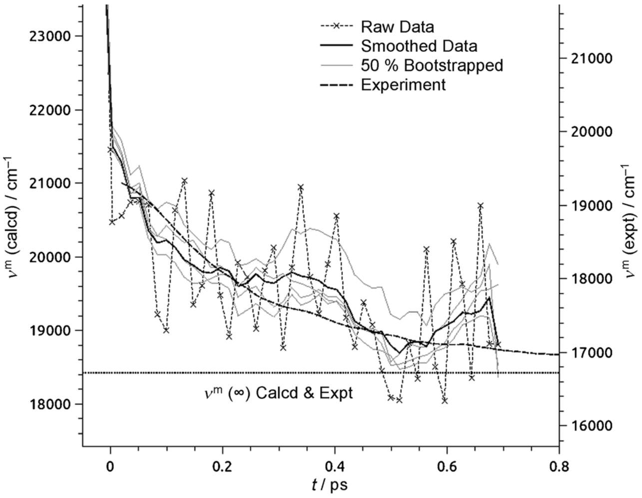

Figure 2. Dynamics of the Stokes shift as obtained by averaging ten trajectories and smoothing by 10 point moving-window averaging (black, left axis), Stokes shift after removal of five random trajectories (gray lines, left axis), experimental data[14] (dashed black line, right axis); data is referenced to $\nu(t{=}\infty)$ in both cases (dotted base line).

around the solute dipole, excitation of MQ reduces the statistical ordering for the water dipoles. This reduction of the ordering due to the weaker dipolar interaction is illustrated in Figure 1 by means of the average orientations of the water molecules around MQ. In the ground state (left) the distribution of water molecules is aligned with the field lines of the MQ dipole, with a reduced amplitude at the nitrogen site. In order to quantify the orientational response of the solvation structure to the excitation of MQ (right), we compute an order parameter λ, inspired by the dipole–dipole interaction energy.

$$\lambda = \left\langle \frac{\varepsilon \cdot \mathbf{p}_{\mathrm{H_2O}}}{\|\varepsilon\| \cdot \|\mathbf{p}_{\mathrm{H_2O}}\|} \right\rangle \qquad \varepsilon = -\nabla\left(\frac{1}{\|\mathbf{r}_{\mathrm{N}} - \mathbf{r}\|} - \frac{1}{\|\mathbf{r}_{\mathrm{O}} - \mathbf{r}\|}\right) \tag{1}$$

For simplicity, we use the geometric orientation of water molecules instead of the actual physical dipoles for $\mathbf{p}_{\mathrm{H_2O}}$ and the electric field ε of point charges at the oxygen and nitrogen atoms. Our first-principles MD simulations yield $\lambda = 0.12$ in the ground state and $\lambda = 0.08$ upon excitation. We find the average vertical $S_0 \rightarrow S_1$ excitation energy to be 2.97 eV—close to the experimental value of 3.04 eV.[13] In the excited state the electronic excitation energy is found to be 2.29 eV, 0.2 eV higher than the experimentally observed value. We attribute this difference to the fact that in our triplet model, the chromophore moves on a slightly different energy surface than in the true S_1 state.

In our simulation, we switch from the ground state to the excited state and then follow the solvent relaxation by means of the vertical de-excitation energy $\nu(t)$. In order to increase ergodicity, we sample from ten independent trajectories started at different points of the equilibrated ground-state trajectory to yield an ensemble average for the evolution of the fluorescence wavenumber $\nu^m(t)$. To provide an estimate of the uncertainty inherent in the limited sampling, we have computed $\nu^m(t)$ based on half of the trajectories (gray lines in Figure 2, multiple random selection of trajectory subset). The time-dependent Stokes shift of our ab initio MD is shown in in Figure 2 (black line). When we correct for the different equilibrium de-excitation energy ν^m_∞ we find good agreement with experiment. The computed Stokes shift exhibits oscillations with a period of about 350 fs, which are not visible in experiment. We believe they may be due to finite size effects.

A complementary approach to characterize solvation dynamics is the relaxation from excited-state equilibrium to ground-state equilibrium. The shape and relaxation time of the reversed time-dependent Stokes shift, that is, an "anti-Stokes" shift, is virtually identical to the fluorescence stokes shift (see Figure S7 in the Supporting Information).

Having obtained a good reproduction of the experimental relaxation, we further decompose the total Stokes shift into several contributions. For the intramolecular part, we compute the Stokes shift using only the isolated MQ in geometries extracted from the (fully solvated) MD trajectory. We find that the de-excitation energy of isolated MQ does not decrease over time; instead it oscillates with a frequency of about 600 cm^{-1}, other modes being less discernible. Experimentally, the intramolecular vibrational modes obtained from the maxima of stimulated emission[8] also are present in this region: prominent peaks occur at 460 cm^{-1}, 520 cm^{-1}, and 600 cm^{-1} (see the Supporting Information).

Shifting from the chromophore to the solvent, the question arises which water molecules provide the largest contribution to the TDSS. The solvation energy difference $\Delta E_{\mathrm{Solv}}(t)$ for a cluster of MQ with surrounding water molecules is just the difference between the $S_1 \rightarrow S_0$ transition energies of the isolated MQ molecule and the cluster; therefore intramolecular oscillations of MQ are mapped out.

We compute $\Delta E_{\mathrm{Solv}}(t)$ of solvent clusters extracted from our trajectories, partitioning the solvating water molecules into three groups (Figure 3): group a: water molecules that are located in a torus 10 Å in diameter centered at the N–O axis of MQ (for details see the Supporting Information);

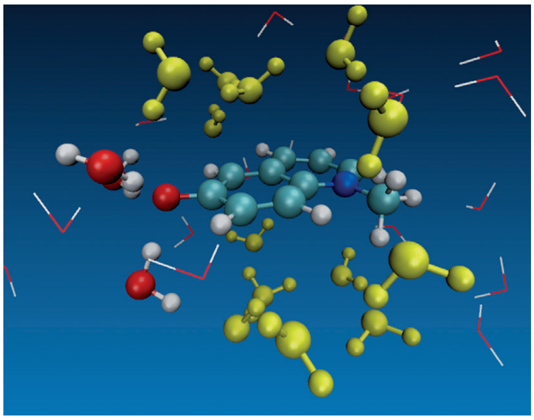

Figure 3. The first solvation shell of MQ and its components: Water molecules in a torus around the N–O axis of MQ (yellow balls, type a in Figure 4), H_2O molecules hydrogen-bonded to the MQ oxygen terminus (red and white balls, type b), and the entire first solvation shell (rods, type c).

group b: water molecules that are hydrogen-bonded to MQ; group c: the full first solvation shell of water. This partitioning of the first solvation shell is motivated by experimental results indicating that the Stokes shift is mostly caused by dipolar relaxation of water molecules.[8] Hence we choose the water molecules in the first solvation shell that are most affected by the change in the dipolar field of MQ.

We find that within the examined clusters, only the water molecules in group a shows considerable net relaxation behavior. The contribution of the water molecules to the Stokes shift amounts to about 0.3 eV, which represents a substantial part of the observed dynamic Stokes shift. For the water molecules in group b we find a strong contribution to the static ΔE_{Solv} (Figure 4, dashed gray line); this molecular solvatochromism is consistent with our previous results.[12] Instead of a relaxation, we find an increase in the solvation energy in first 0.1 ps. Finally, for water molecules in group c no net relaxation is visible after 0.7 ps, despite a strong initial response within the first 0.1 ps.

Summarizing the above, the dielectric effects of MQ solvation clearly extend beyond the first solvation shell, as the complete relaxation of ΔE_{Solv} is considerably larger than the contribution from the first solvation shell only. Extrapolating ΔE_{Solv} of the cluster decompositions, we estimate that the aqueous dielectric screening of the MQ probe extends roughly 8 Å into the solution. When examining the time evolution of the three hydrogen bonds connected to the MQ oxygen, we find that a rapid elongation of these bonds occurs (see the Supporting Information). The weakening of these hydrogen bonds occurs within 0.2 ps after the excitation; this local dynamics could in principle explain the initial Stokes relaxation. However, a direct causality between the geometric motif and the MQ excitation energy is not confirmed by the cluster decomposition (dashed gray line in Figure 4.) Only the full solution is capable of reproducing the experimental relaxation.

In conclusion, our ab initio molecular dynamics simulations in combination with TD-DFT calculations are able to explain the experimentally observed femtosecond time dependence of the fluorescence Stokes shift of solvated *N*-methyl-6-oxyquinolinium betaine at the molecular level. By decomposing the MD trajectories, we show that an important contribution to the time-dependent Stokes shift originates from a group of water molecules that strongly interact with MQ's molecular dipole (located inside a torus around the aromatic core of MQ). Our MD simulations give a molecular, first-principles justification to interpretations based on dipolar relaxation: Molecular excitation of MQ causes a loss of dipolar orientation that extends through the solution, which we describe by a suitable order parameter λ. For the relaxation of the ground state from the excited-state equilibrium, we predict a very similar behavior of the relaxation dynamics. As our method of calculating the time-dependent Stokes shift of MQ does not use any adjustable parameters, it can be readily transferred to more complex systems, in particular biomolecules.

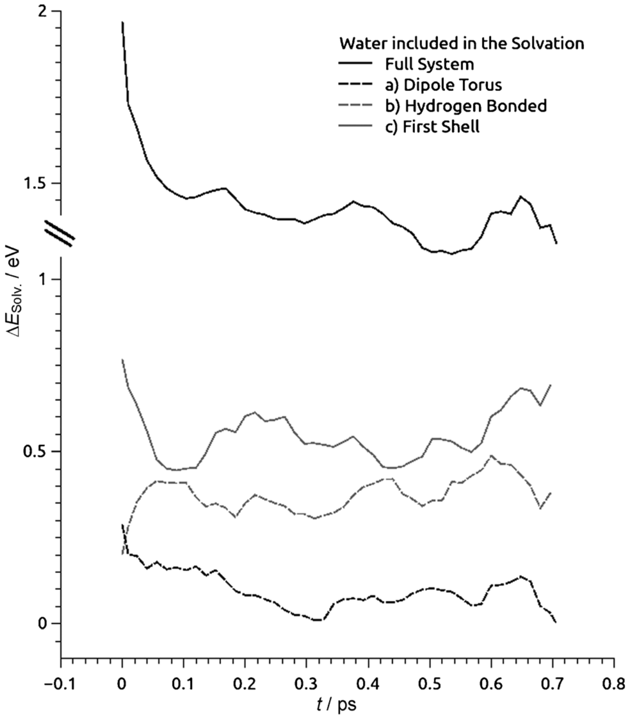

Figure 4. Computed time evolution of the solvation energy $\Delta E_{\mathrm{Solv}}(t)$ for the three types of water molecules around MQ, for the subsystems extracted from the fully solvated MQ trajectory. For definitions of the subsystems see Figure 3 and the main text.

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[1] a) M. Fayer, N. E. Levinger, *Annu. Rev. Anal. Chem.* **2010**, *3*, 89; b) J. C. Rasaiah, S. Garde, G. Hummer, *Annu. Rev. Phys. Chem.* **2008**, *59*, 713.

[2] a) Y. Levy, J. N. Onuchic, *Annu. Rev. Biophys. Biomol. Struct.* **2006**, *35*, 389; b) D. Lucent, V. Vishal, V. S. Pande, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 10430; c) K. M. Ravikumar, W. Hwang, *J. Am. Chem. Soc.* **2011**, *133*, 11766; d) P. Ball, *ChemPhysChem* **2008**, *9*, 2677; e) S. K. Pal, A. H. Zewail, *Chem. Rev.* **2004**, *104*, 2099; f) Y. H. P. Auffinger, *Curr. Opin. Struct. Biol.* **2007**, *17*, 325; g) P. Ball, *Chem. Rev.* **2008**, *108*, 74.

[3] a) K. Ataka, T. Kottke, J. Heberle, *Angew. Chem.* **2010**, *122*, 5544; *Angew. Chem. Int. Ed.* **2010**, *49*, 5416; b) K. Adamczyk, M. Prémont-Schwarz, D. Pines, E. Pines, E. T. J. Nibbering, *Science* **2009**, *326*, 1690.

[4] M. Horch, L. Lauterbach, M. Saggu, P. Hildebrandt, F. Lendzian, R. Bittl, O. Lenz, I. Zebger, *Angew. Chem.* **2010**, *122*, 8200; *Angew. Chem. Int. Ed.* **2010**, *49*, 8026.

[5] a) U. Heugen, G. Schwaab, E. Bründermann, M. Heyden, X. Yu, D. M. Leitner, M. Havenith, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 12301; b) M. Heyden, J. Sun, S. Funkner, G. Mathias, H. Forbert, M. Havenith, D. Marx, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 12068; c) N. E. Levinger, *Science* **2002**, *298*, 1722.

[6] a) M. L. Horng, J. A. Gardecki, A. Papazyan, M. Maroncelli, *J. Phys. Chem.* **1995**, *99*, 17311; b) G. Haran, W.-D. Sun, K. Wynne, R. M. Hochstrasser, *Chem. Phys. Lett.* **1997**, *274*, 365; c) A. Dallmann, M. Pfaffe, C. Mügge, R. Mahrwald, S. A. Kovalenko, N. P. Ernsting, *J. Phys. Chem. B* **2009**, *113*, 15619.

[7] a) K. Dimroth, C. Reichardt, T. Siepmann, F. Bohlmann, *Justus Liebigs Ann. Chem.* **1963**, *661*, 1.

[8] a) J. L. Pérez Lustres, S. A. Kovalenko, M. Mosquera, T. Senyushkina, W. Flasche, N. P. Ernsting, *Angew. Chem.* **2005**, *117*, 5779; *Angew. Chem. Int. Ed.* **2005**, *44*, 5635; b) M. Sajadi, Y. Ajaj, I. Ioffe, H. Weingärtner, N. P. Ernsting, *Angew. Chem.* **2010**, *122*, 464; *Angew. Chem. Int. Ed.* **2010**, *49*, 454; c) J. L. Pérez-Lustres, F. Rodriguez-Prieto, M. Mosquera, T. A. Senyushkina, N. P. Ernsting, S. A. Kovalenko, *J. Am. Chem. Soc.* **2007**, *129*, 5408.

[9] a) V. Barone, J. Bloino, S. Monti, A. Pedone, G. Prampolini, *Phys. Chem. Chem. Phys.* **2011**, *13*, 2160; b) M. Wohlgemuth, V. Bonacić-Koutecky, R. Mitrić, *J. Chem. Phys.* **2011**, *135*, 054105; c) J. Grilj, E. N. Laricheva, M. Olivucci, E. Vauthey, *Angew. Chem.* **2011**, *123*, 4589; *Angew. Chem. Int. Ed.* **2011**, *50*, 4496.

[10] a) J. W. Park, H. W. Kim, C. ik Song, Y. M. Rhee, *J. Chem. Phys.* **2011**, *135*, 014107; b) R. Jimenez, G. R. Fleming, P. V. Kumar, M. Maroncelli, *Nature* **1994**, *369*, 471.

[11] a) M. Böckmann, N. L. Doltsinis, D. Marx, *J. Phys. Chem. A* **2010**, *114*, 745; b) I. Tavernelli, M.-P. Gaigeot, R. Vuilleumier, C. Stia, M.-A. Herv du Penhoat, M.-F. Politis, *ChemPhysChem* **2008**, *9*, 2099; c) P. R. L. Markwick, N. L. Doltsinis, *J. Chem. Phys.* **2007**, *126*, 175102; d) L. Bernasconi, M. Sprik, J. Hutter, *J. Chem. Phys.* **2003**, *119*, 12417; e) M. Iannuzzi, T. Chassaing, T. Wallman, J. Hutter, *Chimia* **2003**, *59*, 499.

[12] C. Allolio, D. Sebastiani, *Phys. Chem. Chem. Phys.* **2011**, *13*, 16395.

[13] E. Bardez, A. Chatelain, B. Larrey, B. Valeur, *J. Chem. Phys.* **1994**, *98*, 2357.

[14] M. Sajadi, M. Weinberger, H.-A. Wagenknecht, N. P. Ernsting, *Phys. Chem. Chem. Phys.* **2011**, *13*, 17768.