

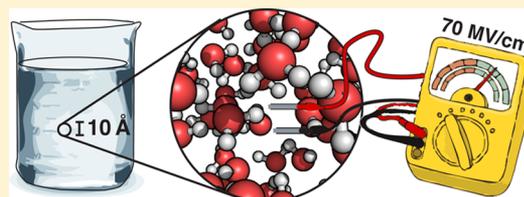
Calculations of the Electric Fields in Liquid Solutions

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S Supporting Information

ABSTRACT: The electric field created by a condensed-phase environment is a powerful and convenient descriptor for intermolecular interactions. Not only does it provide a unifying language to compare many different types of interactions, but it also possesses clear connections to experimental observables, such as vibrational Stark effects. We calculate here the electric fields experienced by a vibrational chromophore (the carbonyl group of acetophenone) in an array of solvents of diverse polarities using molecular dynamics simulations with the AMOEBA

polarizable force field. The mean and variance of the calculated electric fields correlate well with solvent-induced frequency shifts and band broadening, suggesting Stark effects as the underlying mechanism of these key solution-phase spectral effects. Compared to fixed-charge and continuum models, AMOEBA was the only model examined that could describe nonpolar, polar, and hydrogen bonding environments in a consistent fashion. Nevertheless, we found that fixed-charge force fields and continuum models were able to replicate *some* results of the polarizable simulations accurately, allowing us to clearly identify which properties and situations require explicit polarization and/or atomistic representations to be modeled properly, and to identify for which properties and situations simpler models are sufficient. We also discuss the ramifications of these results for modeling electrostatics in complex environments, such as proteins.



1. INTRODUCTION

A molecule in solution experiences a complex range of electrostatic interactions from the solvent molecules in its environment; these interactions play a central role in defining the dynamics and ensemble properties of the liquid solution phase. One way of describing these interactions in a collective fashion is to consider the total electric field they exert on a molecule of interest, or a particular part of that molecule. A key advantage of this electric field picture is that it provides a unifying language for comparing the relative importance of diverse specific interactions such as hydrogen bonds and π -stacking, as well as nonspecific interactions such as dipole–dipole and dipole–induced dipole.

Electric fields can be calculated using models at many different levels of theory^{1–7} and possess a clear connection to experimental observables,^{8–10} especially those involving molecular vibrations.^{11–17} The frequency shifts of certain vibrations have been shown to report on the local electrostatic field experienced by the vibration.^{11,14,17,18} Moreover, the sensitivity of a given vibration's frequency to electric fields can be experimentally calibrated using vibrational Stark spectroscopy,¹⁹ wherein an external electric field of order 10^0 MV/cm is applied onto a vitrified sample containing the vibrational probe of interest, and the resultant effect on the infrared spectrum is recorded.

Over the previous decade, it has been found that several local high-frequency vibrations such as the C=O and C \equiv N stretch respond to electric fields in a linear fashion,^{18–20} obeying the equation

$$\bar{\nu}_{\text{obs}} - \bar{\nu}_0 = -\bar{F} \cdot \Delta\bar{\mu}_{\text{probe}} \quad (1)$$

where $\bar{\nu}_{\text{obs}}$ is the observed frequency of a vibrational probe in a particular environment, \bar{F} is the (absolute) electric field the environment exerts onto the vibrational probe, $\bar{\nu}_0$ is the frequency of the probe in a reference state calibrated to zero electric field, and $\Delta\bar{\mu}_{\text{probe}}$ is the vibrational probe's difference dipole (also called the Stark tuning rate), which is determined by Stark spectroscopy and has values between 0.03–0.1 D/f for different vibrations, translating to field sensitivities of 0.5–1.7 $\text{cm}^{-1}/(\text{MV}/\text{cm})/f$.^{19–21} Where models have been used to assign electric fields to different environments, vibrational frequencies have appeared to maintain linear sensitivity to fields on the order of 10^1 MV/cm.^{11,12} $\Delta\bar{\mu}_{\text{probe}}$ is a vector quantity, though for highly localized modes such as the C=O and C \equiv N stretch, the vibration is assumed to behave as a one-dimensional oscillator, implying that the difference dipole is parallel to the diatomic fragment's bond axis.¹⁹ For a number of vibrational probes we have investigated, the Stark tuning rate has been shown to be largely invariant of the environment's electric field, leading us to consider it an intrinsic property of the oscillator.^{20,22,23} f is the local field correction factor, and its meaning and value is described in the discussion.

This effect has been extended to model frequency shifts observed upon introducing vibrational probes into various condensed-phase environments, such as solvents,^{5,23,24} ionic

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liquids,^{25,26} membranes,^{27,28} and proteins,^{6,13,14,20–23,29} where electric fields arise from local intermolecular interactions. In particular, the suggestion that solvent-induced (optical) frequency shifts are *actually* Stark effects was first voiced by Platt in 1961³⁰ and later elaborated by Liptay.³¹ According to this suggestion, a model for calculating solvent fields (i.e., the electric field the solvent collectively exerts onto a solute) may be able to predict solvent-induced vibrational frequency shifts according to eq 1.

Recent work²³ using molecular dynamics (MD) simulations with a fixed-charge force field has borne out this prediction. In particular, the use of an atomistic representation of the solvent called attention to the electrostatic effects of specific interactions such as hydrogen bonds, showing that their influence on vibrational frequencies is also amenable to an electrostatic interpretation. The C=O frequency shifts of the model solute acetophenone were found to be well explained by the solvent electric field in all solvents examined. However, electronic polarizability is expected to contribute significantly to all intermolecular interactions in solution, suggesting that force fields with explicit treatments of polarization would provide a more accurate and physical description of the condensed phase and the electric fields associated with it.

Solvent fields are important because they attach a quantitative measure to solvation forces, which have long served as useful models for understanding the interactions underlying biomolecular structure and dynamics.^{2,32–34} However, because solvents are composed of many fewer unique constituents than biomolecules, they can benchmark models of condensed-phase effects without the stringent sampling issues or force field complexity characteristic of biological systems. Additionally, solvent fields and solvent-induced frequency shifts can be combined to build field-frequency calibration curves to assist the measurement of electrostatic fields in biomolecular systems, which can establish quantitative connections between molecular structure and biological function.^{23,35}

In the following, we describe simulations of acetophenone dissolved in several solvents and calculate the electric fields the solvents exert on the carbonyl group of acetophenone using the AMOEBA force field. AMOEBA is an atomistic model that incorporates polarizability explicitly by conferring upon each atomic site a point dipole that is induced according to the self-consistent electric field arising from all other sites.³⁶ This additional sophistication in the model influences the calculated solvent fields in a number of important ways. These electric fields are compared to those obtained with the previously published MD simulations using fixed-charge force fields,²³ and two continuum models: the Onsager reaction field,¹ and the Poisson–Boltzmann equation.^{3,4} Results from the fixed-charge force fields and the continuum models share a number of characteristics in common with the AMOEBA solvent fields, but they each differ in characteristic ways. By noting the similarities and differences between solvent fields for acetophenone determined using continuum, fixed-charge, and polarizable models, we can validate which aspects of condensed-phase electrostatic interactions are reproduced by the simpler models, while also calling attention to what properties require explicit polarization or an atomic representation to be consistent with experimental frequency shifts.

2. METHODS

2.1. Simulation Overview. Acetophenone (structure shown in Figure 1A) was placed at the center of a cubic box

filled with solvent molecules. In total, seven solvents were considered: acetonitrile, dibutyl ether, dimethyl sulfoxide, *n*-hexane, tetrahydrofuran, valeronitrile, and water. The aforementioned solvents were chosen on the basis of the separation of acetophenone's C=O vibrational frequency when dissolved in them, implying that they span a large range in electric field and, because they do not contain carbonyl groups, enabling accurate measurements of acetophenone's C=O peak. All simulations were carried out using the Tinker 6.2 molecular modeling package.³⁷ During production dynamics, the electric field experienced by the C=O vibration of acetophenone from the solvent environment was calculated in each snapshot by finding the electric fields at the C-atom and O-atom, projecting them along the C=O unit vector, and then taking the average. This operation is equivalent to the dot product on the right-hand side of eq 1 because for carbonyls, the difference dipole is assumed to be parallel with the C=O bond axis.^{19,38} The electric field defined in this way is denoted $|F_{\text{vib}}|$. The electric field drop along the C=O bond (also referred to as the field drop) is defined as the difference between the projected fields at the C-atom and O-atom and is denoted $|\Delta F_{\text{vib}}|$. The simple procedure devised to calculate electric fields is described in methods section 2.4.

2.2. Parametrization. We used the AMOEBA water model,³⁹ and parameters for acetonitrile and dimethyl sulfoxide were taken from recently published work.⁴⁰ Acetophenone, *n*-hexane, dibutyl ether, tetrahydrofuran, and valeronitrile were parametrized according to the following protocol.

The multipole parameters for *n*-hexane, valeronitrile, and dibutyl ether were taken from the closest relatives in the AMOEBA force field for organic molecules. *n*-Hexane was constructed with the alkane methyl (C and H) and alkane methylene (C and H) atom types. The same four alkane atom types were also used in valeronitrile and dibutyl ether, though atom types in acetonitrile (for valeronitrile) and dimethyl ether (for dibutyl ether) were used as well. For the latter two molecules, small changes ($<0.1e$) were made to the partial charges at the interfacing atoms to enforce charge neutrality. Acetophenone and tetrahydrofuran were assigned multipole parameters de novo using the POLEDIT utility in Tinker 6.2 and following the prescription in the Supporting Information of Ren et al.⁴⁰ Briefly, the procedure involves fitting the ab initio electrostatic potential surface evaluated at the MP2/aug-cc-pVTZ level to a distributed set of multipoles fixed at the nuclear positions.⁴¹ Polarizability and van der Waals parameters were used unchanged from the recommendations in Ren et al.⁴⁰

As for the valence parameters for *n*-hexane, valeronitrile, and dibutyl ether, the majority were taken from the analogous atom types in AMOEBA without modification, similar to the multipole parameters. Torsional parameters that were present in AMOEBA were used without modification; if absent, the corresponding generalized AMBER force field (GAFF) parameter was used.⁴² The valence parameters for acetophenone and tetrahydrofuran were determined using the VALENCE utility in Tinker 6.2. This procedure estimates equilibrium values and force constants by drawing appropriate values from a library, which are then refined by fitting the MM-derived normal-mode frequencies against QM frequencies evaluated at the B3LYP/6-311++G(2d,2p) level^{43,44} with anharmonic corrections.^{45,46} As VALENCE does not automate estimation of torsional parameters, these were taken from the GAFF force field.⁴² These parametrizations were able to reproduce room-temperature liquid densities to within 1–2%

following 100 ps of equilibration. All of the parameters for the solvent molecules are given in the Supporting Information.

2.3. Solvation Simulation Methods. Acetophenone was placed at the center of a cubic box (with edge lengths equal to 45 Å) filled with solvent molecules. Between 8×10^3 and 10×10^3 atoms were needed to fill the volume. These solvent boxes were energy minimized first in GROMACS⁴⁷ using 1000 steps of steepest descent with the GAFF force field,⁴² and then further minimized in Tinker down to a root mean square (rms) energy gradient per atom of 1.0 (kcal/mol)/Å with the AMOEBA force field described above. The minimized coordinates were equilibrated for 100 ps in the *NPT* ensemble with reference temperature and pressure set to 298 K and 1.0 atm, respectively. During equilibration, dynamics were evolved according to the velocity Verlet method using a time-step of 1.0 fs. The temperature was regulated with the Andersen thermostat (with a coupling time of 0.1 ps and reference temperature of 298 K), and the pressure with the Berendsen barostat (with a coupling time of 2.0 ps and reference pressure of 1.0 atm) to facilitate rapid convergence. The particle mesh Ewald method⁴⁸ was used to implement long-range electrostatics, and the real space cutoff distance for Ewald summation as well as for van der Waals interactions was set to 10.0 Å. The convergence threshold applied during computation of self-consistent induced dipoles was 10^{-3} D.

Production runs were started from the final positions and velocities of the equilibration runs and continued for an additional 100–2000 ps during which snapshots were recorded every 10 fs. Two separate production trajectories were carried out for each solvent: a “short” run (ca. 150 ps), which employed stringent simulation settings, and a “long” run (ca. 1500 ps), which sacrificed some precision for speed. The trajectories’ results were compared to ascertain the relative trade-offs between sampling and computational precision. During the short (but more precise) simulations, most of the settings from the equilibration runs were maintained except that the self-consistent induced dipole threshold was set down to 10^{-5} D. Additionally, the Beeman integrator was used,⁴⁹ the temperature was regulated with the Bussi thermostat,⁵⁰ and the pressure was regulated with the Monte Carlo barostat, both with 1.0 ps coupling times. During the long simulations, the RESPA multiple-time scale integrator was used with a time step of 2.0 fs,⁵¹ and the induced dipole threshold was brought up to 10^{-3} D. The fluctuation-suppressing Berendsen barostat was used to maintain compatibility with the RESPA integrator as implemented in Tinker.

2.4. Solvent Field Calculations. We developed the following procedure for extracting electric fields from the instantaneous coordinates of the solvent box. At every step where a snapshot of the atomic coordinates was written, the induced dipole moments were additionally printed to a separate output file. Because atomic polarizabilities are defined as scalars (isotropic) in AMOEBA, the induced dipole at any atomic site is collinear and proportional with the total electric field there, including the contributions from both permanent and other induced moments. The electric field is obtained then simply by dividing the induced dipole (in Debye) of the atom of interest (at either C or O) by that atom’s polarizability parameter (in Å³) and multiplying by 299.79 to convert from D Å⁻³ to MV/cm (the conversion factor is the rescaled speed of light in cgs units).

Electric fields determined in this way will naturally contain Coulombic interactions as well as all polarization effects

because all of these components contribute to the induced dipoles when the potential energy is evaluated. An essential consideration about these total electric fields is that they contain the “self-field” arising from the permanent multipoles on the *same* molecule as the vibrational probe, as well as the self-polarization between distal moieties on the same molecule. These intramolecular contributions lie outside the definition of the electric field that we employ as the electric field *due* to the environment, and our goal is to use the electric field as a descriptor for intermolecular interactions. In our definition, the electric field on any atom in a molecule is necessarily zero when the molecule is isolated in the gas phase. In this way, the electric field due to the environment uses the isolated molecule in the gas phase as the reference state.

To remove the contribution of the self-field from the total field, we took every snapshot during solvent dynamics and stripped away all the solvent molecules, leaving acetophenone in its instantaneous configuration at that moment in the trajectory. The induced dipoles on the atoms of interest for the solute-only system were evaluated (without running dynamics) and converted into electric fields. This field was subtracted from the corresponding field from the trajectory, to admit the electric field due to the environment; i.e., the solvent field. Mathematically, these steps correspond to

$$\vec{F}_{\text{tot}}^i = \vec{\mu}_{\text{ind,tot}}^i / \alpha^i \quad (2)$$

$$\vec{F}_{\text{self}}^i = \vec{\mu}_{\text{self,tot}}^i / \alpha^i \quad (3)$$

$$\vec{F}^i = \vec{F}_{\text{tot}}^i - \vec{F}_{\text{self}}^i \quad (4)$$

$$|F_{\text{vib}}| = \frac{1}{2}(\vec{F}^{\text{C}} \cdot \hat{u}_{\text{CO}} + \vec{F}^{\text{O}} \cdot \hat{u}_{\text{CO}}) \quad (5)$$

$$|\Delta F_{\text{vib}}| = (\vec{F}^{\text{O}} \cdot \hat{u}_{\text{CO}} + \vec{F}^{\text{C}} \cdot \hat{u}_{\text{CO}}) \quad (6)$$

In eqs 2–4, i indexes over the C-atom and O-atom of the carbonyl probe, α^i is the atomic polarizability of the i th atom, and μ_{ind}^i is the induced dipole of the i th atom. In eq 2, the total electric field on atom i , \vec{F}_{tot}^i , is calculated by including all atoms in the solvent-box (as they are during the simulation), whereas in eq 3, the self-field, \vec{F}_{self}^i , is found by isolating the solute. The difference in eq 4 filters off the self-field contribution, leaving the desired electric field due to the environment. Finally, the electric field experienced by the vibration is found by projecting along the C=O bond vector and averaging (eq 5), and the electric field drop by projecting and subtracting (eq 6) as mentioned previously. Implementation of this method is described in detail in Supporting Information methods.

2.5. Poisson–Boltzmann Calculations. The Poisson–Boltzmann (PB) equation is a prescription for calculating the electrostatic potential for an arbitrary charge density and dielectric map:

$$-\vec{\nabla} \cdot (\epsilon(\vec{x}) \vec{\nabla} \phi(\vec{x})) + \kappa^2(\vec{x}) \sinh \phi(\vec{x}) = \rho(\vec{x}) \quad (7)$$

where $\epsilon(\vec{x})$, $\phi(\vec{x})$, $\rho(\vec{x})$, and $\kappa(\vec{x})$ are the position-dependent dielectric, electrostatic potential, charge density, and ionic strength respectively. Equation 7 provides a general way of calculating the electrostatic properties of a system composed of one region that is represented atomistically (via atomic coordinates and charges, $\rho(\vec{x})$), and another region that is represented implicitly (via a position-dependent dielectric function, $\epsilon(\vec{x})$).⁵² PB models are important to examine

Table 1. Electric Fields in Seven Solvents Calculated by MD with the AMOEBA Force Field

solvent	simulation time/ps ^a	$ F_{\text{vib}} /(\text{MV}/\text{cm})^b$		$ \Delta F_{\text{vib}} /(\text{MV}/\text{cm})^c$	
		mean	std dev	mean	std dev
<i>n</i> -hexane	181.4	-10.91 ± 0.37	4.91	-6.98 ± 0.21	5.20
dibutyl ether ^d	106.2	-24.16 ± 1.74	10.49	-16.60 ± 1.25	10.98
tetrahydrofuran	151.0	-30.63 ± 1.47	9.95	-18.53 ± 2.13	10.56
valeronitrile	181.6	-35.73 ± 1.54	12.49	-23.16 ± 1.76	12.72
acetonitrile	240.1	-36.11 ± 0.82	12.69	-25.10 ± 0.45	12.49
dimethyl sulfoxide	171.8	-42.85 ± 1.38	13.39	-26.49 ± 0.70	12.60
water	110.7	-69.50 ± 3.04	26.12	-51.88 ± 3.89	25.00

^aData reflect results from the stringent (short) simulations of acetophenone in a box filled with various solvents. Electric fields were sampled every 10 fs. ^bThe electric field experienced by the C=O bond, as defined by eq 5. ^cThe electric field drop over the C=O bond, as defined by eq 6. ^dDibutyl ether exhibits uniquely slow dynamics, implying that these data do not reflect a converged ensemble (see Figure S1 (Supporting Information) and analysis).

alongside fully atomistic approaches because they are used to model solvents inexpensively as continua, and it forms the theoretical framework for implicit solvation models, which greatly reduce the number of explicit atoms needed in a simulation.^{53,54} We represented acetophenone as an optimized configuration of atoms bearing GAFF force field point charges, and the solvent as a polarizable continuum. As the PB approach intrinsically averages over solvent degrees of freedom, and the solvent field is largely independent of the solute configuration, we carried out single-point calculations. The solute molecule was enclosed by a surface defined by the atomic radii parameters optimized by Swanson et al. for smoothed surfaces,⁵⁴ inside of which an internal (solute) dielectric of 2 was designated, and outside of which was designated a medium whose dielectric was set equal to the experimental static dielectric constant⁵⁵ of each of the seven solvents examined. The full PB equation was solved numerically on a cubic grid with a mesh spacing of 0.25 Å using the APBS software package⁴ with point charges smoothed via cubic B-splines, whereas the dielectric bounding surface was smoothed with a seventh order polynomial. The latter two options are necessary for accurate calculations of electrostatic forces.^{54,56} The calculated electrostatic forces experienced by the C and O atoms (in $\text{kJ mol}^{-1} \text{Å}^{-1}$) were divided by their respective charges (in elementary charges) and multiplied by 1.03627 to give the local electric field on each atom in units of MV/cm. This electric field is dominated by a self-field from the solute's charges, which we remove by performing a reference calculation in which the solvent dielectric is set to 1 and the internal dielectric is maintained. The reference calculation isolates the self-field, and the difference between the total field and the self-field, analogous to eq 4, gives the electric field due to the solvation environment. The electric field experienced by the vibration and the electric field drop were calculated according to eqs 5–6, as specified above.

3. RESULTS

3.1. Average Electric Fields in Solution. Ensemble averages and standard deviations of each solvent's electric field as calculated with the AMOEBA simulations are reported in Table 1. Here and in the following, the values reported reflect those from the short simulations; data from the long simulations are recorded in Table S2, Supporting Information. The average electric field in the nonpolar solvent, *n*-hexane, was $-10.9 \text{ MV}/\text{cm}$. The negative sign associated with the electric field implies an overall energetically favorable interaction between the C=O moiety and its environment. Throughout

the trajectories, there were a few snapshots in which the instantaneous field exerted on C=O was positive, though these were rare (less than 1% of snapshots for all solvents), and they contribute little to the ensemble average.

Solvents of increasing polarity were found to exert increasingly large electric fields, with dimethyl sulfoxide (DMSO) exerting $-42.8 \text{ MV}/\text{cm}$ onto C=O. Water, which is capable of forming hydrogen bonds (H-bonds) to C=O, was associated with the largest solvent field ($-69.5 \text{ MV}/\text{cm}$) by a considerable margin. The large electric field attendant upon formation of an H-bond can be explained by considering the fact that O–H bonds have large bond dipole moments, and due to the small size of the hydrogen atom, they can approach the C=O bond very closely. The electric field due to a dipole decays as the inverse *cube* of the distance, so small changes in distance are significant.

The vibrational frequency of the C=O bond is known to be a sensitive reporter of its local environment and its solvatochromic trends have been extensively explored by using empirical solvent polarity scales.^{57–60} According to Figure 1A (boxes), the solvent-induced frequency shifts are also well explained by the average electric field each solvent exerts onto the vibration, a preferable explanatory variable due to its more fundamental nature. The relationship produces a regression line with form $\bar{\nu}_{\text{C=O}} = 0.484\langle|F_{\text{vib}}|\rangle + 1703.6$. In this regression, the slope represents the sensitivity of the vibrational frequency to field, corresponds to the magnitude of $\Delta\bar{\mu}$ from eq 1, and can be compared to the empirical Stark tuning rate; the intercept represents a reference frequency associated with zero electric field, corresponds to $\bar{\nu}_0$ from eq 1, and can be compared to the empirical vibrational frequency of acetophenone in the gas phase, *vide infra*.

The average electric fields determined with the long trajectories are generally 10–20% smaller than those for the short. The difference is statistically significant, as the correlation-adjusted errors in the average electric fields are between 3 and 5% for most of the solvents, suggesting that longer trajectories can better sample energetically unfavorable configurations that bring down the ensemble-averaged field magnitudes. Nevertheless, the difference is small, suggesting that the electric fields have mostly converged by 100 ps of sampling. Finally, the slope and intercept of the field-frequency model constructed with the fields from the long trajectories ($0.507 \text{ cm}^{-1}/(\text{MV}/\text{cm})$ and 1702.6 cm^{-1} , respectively) are within the estimates of the error of the regression line parameters in Figure 1A ($\pm 0.03 \text{ cm}^{-1}/(\text{MV}/\text{cm})$ and $\pm 1.2 \text{ cm}^{-1}$, respectively). We chose to focus on the short trajectories

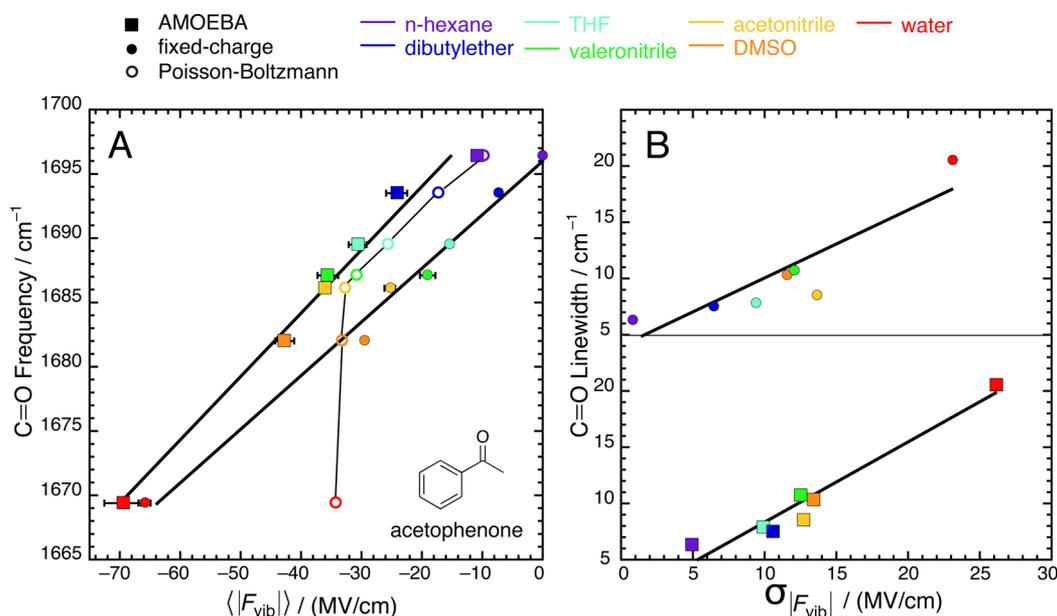


Figure 1. Correlation between calculated electric fields and properties of the C=O vibration on acetophenone for seven solvents (data given in Tables 1 and 2). Squares represent electric fields from simulations with the AMOEBA force field, closed circles represent electric fields from simulations with a fixed-charge force field,²³ and open circles represent electric fields from solving the Poisson–Boltzmann equation. (A) Peak vibrational frequency correlates strongly with average electric field. (B) Full-width at half-maximum (line width) correlates moderately with electric field standard deviation. In (A), the regression line is $\bar{\nu}_{\text{C=O}} = 0.484\langle |F_{\text{vib}}| \rangle + 1703.6$ with $R^2 = 0.98$ for AMOEBA, and $\bar{\nu}_{\text{C=O}} = 0.412\langle |F_{\text{vib}}| \rangle + 1695.9$ with $R^2 = 0.99$ for fixed-charge. Estimates of the standard error for the slope and intercept are 0.0029 and 1.2 for AMOEBA, and 0.0020 and 0.6 for fixed-charge. For Poisson–Boltzmann, $R^2 = 0.6$, and the trace is a guide to the eye, not a regression. In (B), the regression line is $\text{LW}_{\text{C=O}} = 0.714\sigma |F_{\text{vib}}| + 1.14$ with $R^2 = 0.94$ for AMOEBA, and $\text{LW}_{\text{C=O}} = 0.626\sigma |F_{\text{vib}}| + 3.46$ with $R^2 = 0.8$ for fixed-charge.

in the main text because they admitted a regression line with a slightly higher R^2 (0.98 compared to 0.96).

The average electric fields are similar to some extent to what we previously calculated using analogous methods and a fixed-charge force field (Figure 1A, closed circles).²³ Where we refer to a fixed-charge force field, parameters for organic molecules came from the generalized AMBER force field (GAFF) as given by Coleman et al.,⁴² water was described by the TIP3P model,⁶¹ and the potential function's form was that used in AMBER. In particular, the fixed-charge model was equally capable of describing the change in average electric field associated with solvent polarity, as reflected in the similarity of the increase in electric field passing from *n*-hexane to DMSO (32.0 MV/cm for AMOEBA and 29.5 for fixed-charge), and the similarity of the two models' slopes in Figure 1A (0.412 and 0.484 $\text{cm}^{-1}/(\text{MV/cm})$). The most obvious difference is that the fixed-charge model assigns the nonpolar solvent *n*-hexane an electric field almost equal to zero, whereas AMOEBA assigns it a significant favorable field. This deviation becomes less pronounced in more polar solvents, such that the AMOEBA water model and the TIP3P model assign water an identical average electric field within error. This effect can clearly be seen by observing that the two regression lines in Figure 1A approach each other and converge near water's electric field.

On the other hand, the PB equation (Table 2 and open circles in Figure 1A) predicts an electric field in *n*-hexane that is virtually identical to the ensemble-averaged field calculated with AMOEBA simulations. For the solvents of relatively low polarity (up to acetonitrile), the PB equation agrees impressively with AMOEBA to within 1–5 MV/cm. The increase in solvent field from *n*-hexane to DMSO is 23.5 MV/cm, in qualitative agreement with the all-atom models, although the agreement is stronger if one considers the span between *n*-

Table 2. Electric Fields in Seven Solvents Calculated by Solving the PB Equation

solvent (static dielectric)	$ F_{\text{vib}} /(\text{MV/cm})^a$	$ \Delta F_{\text{vib}} /(\text{MV/cm})^b$
<i>n</i> -hexane (1.78)	−9.87	−0.91
dibutyl ether (3.08)	−17.39	−1.05
tetrahydrofuran (7.43)	−25.71	−0.49
valeronitrile (20.04)	−30.91	0.62
acetonitrile (37.50)	−32.81	1.44
dimethyl sulfoxide (46.84)	−33.33	1.72
water (78.54)	−34.38	2.26

^aThe electric field experienced by the C=O bond, as defined by eq 5.

^bThe electric field drop over the C=O bond, as defined by eq 6. Note that these electric fields are from single-point calculations (not averages across a trajectory).

hexane and acetonitrile (Figure 1A). However, the PB equation predicts almost no increase in electric field for the two most polar solvents (DMSO and water) over acetonitrile, failing to explain the large bathochromic shifts associated with these solvents. The sudden nonlinear behavior of the curve for the PB model past acetonitrile (Figure 1A) can be attributed to the well-known fact that continuum solvent models omit the effect of specific interactions such as H-bonds. However, the present data afford two additional insights. First, despite the fact that DMSO has no clear H-bond donating capacity, it appears to form some kind of specific interaction as based on the larger PB–AMOEBAs discrepancy (10 MV/cm); and second, for water, the error incurred by omitting the effect of H-bonding is quite severe.

3.2. Heterogeneity of Electric Fields in Solution. Whereas AMOEBA and fixed-charge models appear to be largely in agreement regarding the average properties of the

electric field in solution, especially for polar solvents, they contrast strikingly with regard to the field heterogeneity.

The standard deviation of the electric field distribution reflects the field's temporal heterogeneity over the trajectory and is one contributor (though often the dominant one) to the infrared band's line width because inhomogeneous broadening results from an oscillator sampling different environments (electric fields). Figure 1B shows the relationship between line width and the solvent field distribution's standard deviation; the data for AMOEBA and the fixed-charge models are vertically displaced for clarity. AMOEBA predicts, on the whole, a more widely spread distribution. The fixed-charge–AMOEBAs discrepancy is largest for *n*-hexane and becomes less significant for more polar solvents. More significantly, the fixed-charge model generated field spreads that correlate rather poorly with line width (R^2 of 0.80), whereas the correlation coefficient using the AMOEBA model (0.94) is quite good. This finding suggests that AMOEBA captures the heterogeneity characteristic of each solvent more accurately.

Spatial heterogeneity is represented by differences in the electric field at two separate points, rather than at two different times. A measure of spatial heterogeneity that is pertinent to the C=O vibration is the electric field drop along the bond-length, as defined by eq 6, and shown in Tables 1 and 2. AMOEBA predicts significant field drops in all seven of the solvents studied, and the magnitude of the field drop systematically increases with solvent polarity (Figure 2).

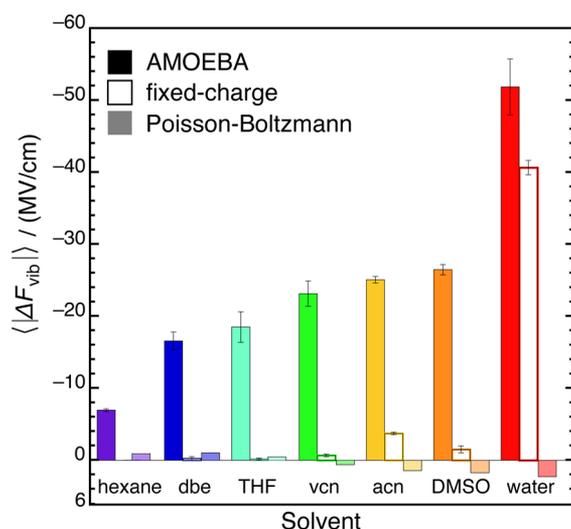


Figure 2. Average electric field drop across the C=O bond for seven solvents (see eq 6 for definition), calculated from simulations with the AMOEBA and fixed-charge force fields and from solving the Poisson–Boltzmann equation. Fixed-charge models predict very homogeneous fields, with drops close to zero, except in water. AMOEBA predicts field drops increase monotonically with solvent polarity, and a very large field drop in water. The Poisson–Boltzmann equation predicts relatively homogeneous fields, and sometimes inverts the sign of the field drop.

These results are strikingly different from those obtained with a fixed-charge model,²³ which predict an essentially homogeneous electric field along the C=O bond in solvents except for water. The large electric field drop created by water can be explained by considering that the sizable fields in this environment are due to H-bonds, which are highly local interactions that are principally mediated through the H-bond

accepting O-atom. Essentially, the “extra” electric field water exerts over DMSO is mostly due to the one or two water molecules in close contact with the O-atom on the solute. On the other hand, the fixed-charge model predicts that all the other (aprotic) solvents produce small field drops along the C=O bond.

The continuum PB-based approach predicts very small electric field drops for all solvents (Figure 2), and in a few cases (including water) predicts the electric field to be larger on the C-atom than on the O-atom. This sign inversion is qualitatively inconsistent with physical intuition. It is apparent that the PB equation does not describe the spatial heterogeneity of the solvent's interactions well because the solvent degrees of freedom are effectively all integrated out.

From comparing these three approaches, one might suggest that the electric field heterogeneity is a qualitative measure of the specificity of a given solvent's interactions. Continuum models, which omit specific interactions, naturally predict electric field drops to be close to zero. In a fixed-charge all-atom model, the concept of an H-bond emerges, marked by the appearance of a highly heterogeneous field along the C=O bond. H-bonds are represented in a binary way though, as the non-H-bonding solvents all have small field drops. The AMOEBA model presents a more nuanced picture in which H-bonds are still the source of the largest field drops, but the binary character of H-bonding is replaced with a spectrum in which solvents of intermediate polarity produce field drops of intermediate magnitude.

3.3. Dynamics of Electric Fields in Solution. Field–field autocorrelation functions were calculated from the long polarizable trajectories. Correlation functions calculated from the short polarizable trajectories were noisy (intense sampling is required to obtain converged correlation functions), whereas correlation functions calculated from trajectories using fixed-charge models generally displayed oscillatory features that resulted in poor fits to exponential decay functions. For all the long polarizable simulations, the correlation decays could be fit well to a double exponential decay (R^2 's between 0.98 and 0.99) but could not be fit well to a single exponential decay (R^2 's between 0.87 and 0.95). The parameters of these fits are compiled in Table 3, and Figure 3 displays field–field autocorrelation functions for three solvents (dibutyl ether, DMSO, and water) at early lag times. The time constants from this analysis correspond roughly to how long it takes the solvent to randomize its structure, using the electric field as a proxy for the collective solvation coordinate.⁶² According to the linear Stark equation (eq 1), the instantaneous vibrational frequency is proportional to the electric field that the vibration experiences, implying that the field–field correlation function effectively encodes the frequency–frequency correlation function, which can be interrogated experimentally by 2-D IR.^{15,63}

Six of the seven solvents examined in this study shared common dynamical characteristics. The solvents universally possess a fast process with a time constant of about 100 fs that accounts for about half of the total dephasing. In the nitrile-based solvents (acetonitrile and valeronitrile), the weight of this fast component is greater. After 100 fs, each solvent exhibits a second slower process with time constants that are more idiosyncratic to each solvent, with *n*-hexane and water being on the faster side (ca. 900 fs), and tetrahydrofuran and valeronitrile on the slower end (ca. 2.5 ps). Qualitatively, the more polar solvents exhibit a faster second decorrelation time scale (a trend that has been observed empirically⁶⁴), although *n*-hexane stands

Table 3. Fitting Parameters of the Electric Field Autocorrelation Functions for the C=O Vibration in Seven Solvents^a

solvent	simulation time/ps ^b	R ²	fast process		slow process		offset
			Δ_1/ps^{-2}	τ_1/ps	Δ_2/ps^{-2}	τ_2/ps	Δ_0/ps^{-2}
<i>n</i> -hexane	1008	0.98	0.640	0.108	0.242	0.861	0.051
dibutyl ether	1402	0.99	0.430	0.162	0.310	4.57	0.237
tetrahydrofuran	1242	0.99	0.553	0.151	0.452	2.30	0.006
valeronitrile	986.3	0.99	0.611	0.141	0.431	2.84	-0.031
acetonitrile	1895	0.99	0.898	0.112	0.167	1.11	0.020
dimethyl sulfoxide	1361	0.99	0.696	0.104	0.317	1.99	0.022
water	699.8	0.98	0.432	0.080	0.465	0.928	0.041

^aAutocorrelation functions were calculated for the field experienced by the vibration ($|F_{\text{vib}}|$), and then fit to the function: $C_{\text{FF}}(t) = \Delta_0 + \Delta_1 \exp(-t/\tau_1) + \Delta_2 \exp(-t/\tau_2)$. ^bData reflect results from the long (less stringent) simulations of acetophenone in a box filled with various solvents. Electric fields were sampled every 10 fs. Fits were carried out on the first 10 ps of the correlation function, after which the correlation function mostly oscillated around zero.

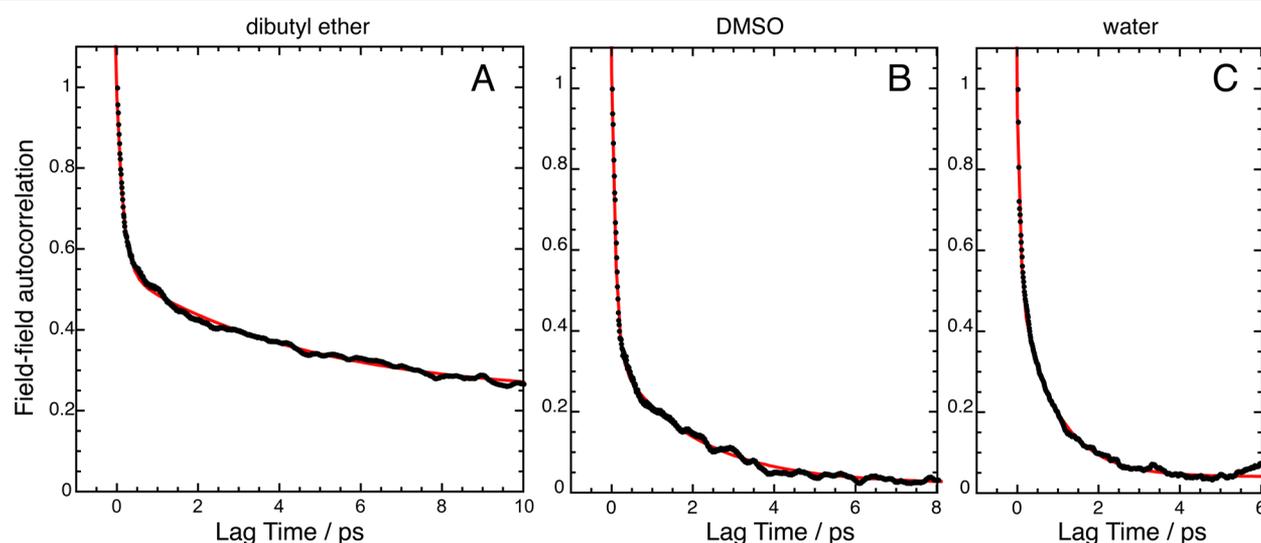


Figure 3. Normalized electric field autocorrelation functions of the C=O vibration on acetophenone in three different solvents: (A) dibutyl ether; (B) dimethyl sulfoxide; (C) water. Black dots represent the autocorrelation data points, and the red trace represents a fit to a double exponential decay. In all cases, the data could not be fit well to a single exponential decay. Fit parameters for all solvents are given in Table 3. The solvents examined share a characteristic time constant for fast dephasing (~ 100 fs) but have different time constants for the slow dynamics. Dibutyl ether is the only solvent with a significant offset, consistent with the 100 ps trajectory not reflecting the true ensemble average (see footnote *d* in Table 1).

out as a clear exception. Finally, all but one of the solvents (dibutyl ether) possess offsets very close to zero, implying that most of the dynamics can fully relax within 10 ps. The fast dynamics is consistent with the good agreement between results from the short and long trajectories, mentioned earlier.

One solvent (dibutyl ether) displayed very different behavior from all the others. It shares the same fast time scale process with the other solvents, but afterward, its fields dephase slowly, with a second time constant of 4.6 ps. Moreover, the presence of a large offset of 0.237 implies that there is a significant contribution from slow dynamics on the tens of picoseconds time scale. Indeed, simple visualization of the field trajectory for dibutyl ether (Figure S1, Supporting Information) confirms the presence of electric fields altering between distinct average values over long periods. The presence of slow dynamics complicates reliable determination of ensemble-averaged properties, which may explain in part why the data point for dibutyl ether fell somewhat off the regression line in Figure 1A.

4. DISCUSSION

4.1. Comparison between AMOEBA and Fixed-Charge Models.

The most obvious differences between the solvent

fields calculated using a polarizable model versus a fixed-charge model is the presence of moderately large electric fields in the nonpolar solvent *n*-hexane. The origin of this field is relatively simple to rationalize: it reflects the polarization that the C=O fragment's permanent dipole induces in the surrounding medium's electron density, which then exercises a field back onto the C=O group. Clearly, explicit polarization is required to capture this effect. The "extra" ~ 10 MV/cm attributed to C=O's polarization of its environment results in larger discrepancies with the fixed-charge model for the nonpolar solvents. To what extent is this ~ 10 MV/cm physically meaningful or an artifact associated with the reference state? To address this question, we note that the intercept of Figure 1A (1703.6 cm^{-1}) compares favorably with the C=O frequency of acetophenone as a vapor (1703 cm^{-1} ^{57,65}). The similarity of these numbers is impressive and suggests that the AMOEBA model consistently describes (and can connect) the gas phase and condensed phase.

As polarity of the solvent increases and a larger portion of the solvent field arises instead from permanent dipoles of the solvent (rather than induced), the percent discrepancy between the AMOEBA and fixed-charge force fields becomes smaller, and in the most polar solvent, the models agree to within 5%.

This observation highlights quite clearly that explicit polarizability is most needed at an interface between a polar and a nonpolar molecule (e.g., acetophenone and *n*-hexane).⁶⁶ As an aside, proteins are often characterized by a delicate interplay between nonpolar and polar moieties, which would suggest that electrostatic interactions in proteins might also demand an explicitly polarizable model to be properly described.

For homogeneous systems, i.e., systems in which all the molecules are either polar or nonpolar, the fixed-charge model reproduces AMOEBA's electric fields, implying that it is capable of reproducing electronic polarization effects on average. By "absorbing" the polarization effect into the charges, fixed-charge force fields include polarization in a mean field sense.⁶⁷ In nonhomogeneous systems, the role of polarization is context-dependent and cannot be programmed into the charge parameters effectively; in these situations, we believe the fixed-charge model gives qualitatively incorrect results, on the basis of its inconsistency with the sizable empirical frequency shift between acetophenone in the gas phase and in *n*-hexane.

4.2. Comparison between AMOEBA and PB Models.

The PB equation predicts a nonzero field in *n*-hexane, producing a value that is almost identical to AMOEBA's. The magnitude of a particular solvent's electric field in a continuum model is determined by the solvent's dielectric constant; because the dielectric constant naturally reflects electronic as well as orientational degrees of freedom, continuum models are particularly well suited for describing the induced interactions between a polar molecule in a nonpolar environment. The overall scale of the solvent fields depends on how close the polarizable medium can get to the solute atoms (the radius parameters⁵⁴) and how strongly the solute atoms can polarize the surrounding medium (the charge parameters⁴²). From noting AMOEBA's and PB's strong agreement for five of the seven solvents examined, this work demonstrates that the PB equation (when equipped with optimized charge and radius parameters) reproduces the scale and the trends in solvent fields of a much more expensive polarizable/atomistic model, at least for simple systems.

On the other hand, because the PB model (and continuum models in general) cannot describe the effects of specific interactions like H-bonds, it predicts the electric field in water to be about half what the TIP3P and AMOEBA water models estimate. Although a different set of dielectric settings (Tables S3 and S4, Supporting Information) or solute charges (Tables S5 and S6, Supporting Information) can produce an electric field for water that agrees somewhat better with the atomistic models, we point out that for *any* choice of the charge, radius, or dielectric parameters, the PB equation will predict similar electric fields for DMSO and water, which is qualitatively incorrect, on the basis of the large empirical frequency shift between acetophenone in DMSO and in water. Therefore, PB's underestimation of electric fields in water cannot be fixed in a physically consistent way. These findings intimate at potential limitations to implicit solvation schemes for MD simulations on proteins, in which modified forms of the PB equation are employed to model the aqueous environment.⁵² The average electric field and the electric field drop may prove to be useful physical properties to parametrize against to produce implicit solvent models that better account for water's distinctively strong and heterogeneous electrostatic interactions.

From inspecting all three models in Figure 1A, it is apparent that the continuum and fixed-charge models exhibit complementary weaknesses. Whereas the fixed-charge model can aptly

describe specific interactions (and attendant large fields), it gives pathological results in nonpolar solvents (small fields); the continuum model excels at describing nonpolar solvents but gets worse at describing more polar solvents, producing qualitatively unphysical results once H-bonds are involved. This point is expressed visually in Figure 1A, where the AMOEBA and PB traces track closely onto one another around *n*-hexane but diverge going out to larger fields.

4.3. Comparison to the Onsager Model. For a solute modeled as a point dipole (of magnitude μ_0) in a spherical cavity, the PB model can be mapped onto a simple analytic expression.¹ With these simplifications, the average solvent field is given by the Onsager reaction field:⁶⁸

$$|F_{\text{Onsager}}| = \frac{\mu_0}{a^3} \left[\frac{2(\epsilon - 1)(n^2 + 2)}{3(2\epsilon - n^2)} \right] \quad (8)$$

In eq 8, n is the solute's refractive index and a is the cavity radius, which is typically estimated from the molecule's density and formula weight. Following this prescription, electric fields were calculated using the Onsager model and are compared against the fields calculated with AMOEBA and PB in Figure 4.

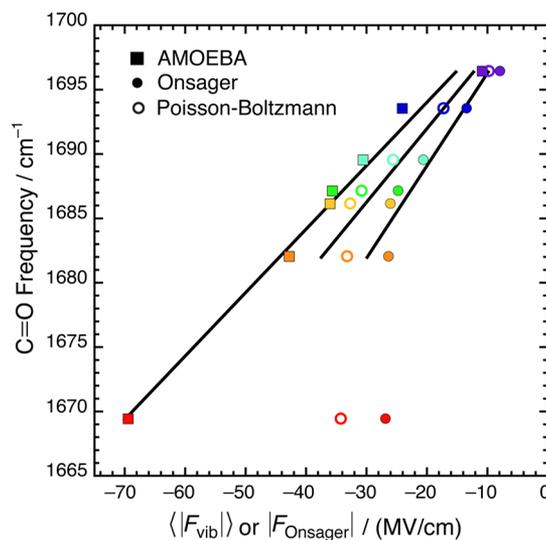


Figure 4. Comparison between the average electric field predicted by AMOEBA, the Poisson–Boltzmann equation, and the Onsager model for seven solvents (see Figure 1 for color code). AMOEBA fields are reproduced from Figure 1 with error bars removed for clarity. The Onsager fields are calculated from eq 8 using $\mu_0 = 2.95$ D, $n^2 = 2.35$, and $a^3 = 46.3$ Å³. Excluding water, the regression line is $\bar{\nu}_{\text{C=O}} = 0.657|F_{\text{Onsager}}| + 1702.2$ with $R^2 = 0.91$ for Onsager and $\bar{\nu}_{\text{C=O}} = 0.526\langle |F_{\text{vib}}| \rangle + 1702.2$ with $R^2 = 0.92$ for PB.

As they are both continuum models, the Onsager and PB models exhibit qualitatively the same behavior, describing the solvents of lower polarity well, but systematically underestimating the fields in the most polar solvents. The overall scale of the solvent fields in the Onsager model is smaller than the PB model's. Because the cavity radius is an ad hoc parameter, especially for nonspherical molecules such as acetophenone, it is reasonable that the Onsager model's predictions for the overall scale will be only approximate. The PB equation estimates the scale of solvent fields in better agreement with AMOEBA (note that the PB trace is closer to AMOEBA's than the Onsager trace) presumably because the cavity's structure is accounted for explicitly. If water is excluded,

the regression lines associated with the continuum models become more meaningful: the slope for the PB model's regression line ($0.526 \pm 0.08 \text{ cm}^{-1}/(\text{MV}/\text{cm})$) is within error of AMOEBA's, whereas the Onsager model produces a slope of $0.657 \text{ cm}^{-1}/(\text{MV}/\text{cm})$. Nevertheless, the ratio $|F_{\text{DMSO}}|/|F_{\text{hexane}}|$ is independent of the cavity radius so it serves as a better basis for evaluating the Onsager model; Onsager predicts this ratio to be 3.3, which is almost the same as PB (3.4) and in qualitative agreement with AMOEBA (3.9).

4.4. Comments on the Electric Field Calculation. The difference calculated in eq 4 results in what we call the electric field due to the environment. This electric field includes the field due to all the permanent multipoles on the solvent atoms, as well as the field due to all the induced dipoles on the solvent atoms, induced by the presence of both the solute and the solvent molecules. Explicitly, it does *not* include the field due to the solute's own permanent multipoles, nor the field due to the induced dipoles on the solute atoms induced by the solute atoms (the molecule's self-polarization). However, the electric field *does* include the contributions from the induced dipoles on solute atoms due to the presence of the solvent molecules. We call this subtle contribution the difference self-field, as it refers to the change in the molecule's self-field imparted by the solvent. The same reference state obtained with AMOEBA by removing the solvent molecules is established in the PB model by setting the solvent dielectric to 1. However, when the solute (internal) dielectric is maintained at 2 in the reference state, the difference self-field is properly evaluated as self-polarization is discarded along with the fields from the solute's permanent charges. We found that reference calculations employing a homogeneous dielectric (i.e., solute and solvent dielectrics set equal) led to poorer agreement with AMOEBA's electric field predictions (see Tables S3 and S4, Supporting Information).

The separation between a molecule and its environment becomes subtle in a polarizable model, although it is achievable if one carefully defines the reference state. We believe that the electric fields reported in this paper are coming close to reflecting the *absolute* magnitudes of the electric fields in liquid solutions (within the scope of the adopted definition). Indeed, the electric fields we calculated for water ($-69.5 \text{ MV}/\text{cm}$) and tetrahydrofuran ($-30.6 \text{ MV}/\text{cm}$) agree excellently with those calculated using QM/MM methods ($-69.8 \text{ MV}/\text{cm}$, $-28.5 \text{ MV}/\text{cm}$ respectively),⁷ with the caveat that the QM/MM work focused on a different solute (acetonitrile); solvent fields also depend on the *solute's* identity because the solvent field fundamentally reflects a reorganization process of the solvent reacting to the solute.¹ The close correspondence between the gas-phase C=O frequency for acetophenone and the intercept of AMOEBA's and PB's field-frequency curves also supports this claim.

Using the method described above to calculate fields from AMOEBA simulations, the desired electric fields, \vec{F}^i , are of the same order of magnitude as \vec{F}_{self}^i (and generally within a factor of 2). In other words, the calculated solvent fields are not tiny portions on top of the self-fields, averting a dilemma in which we would have to take the difference between two large numbers with close values. This feature is not trivial because molecules' self-fields arising from their own nuclei and electrons are actually *very* large (of order $\sim 10^3$ – $10^4 \text{ MV}/\text{cm}$); the reason this behavior is not found in the present calculations is that AMOEBA excludes Coulombic interactions between multipoles and damps self-consistent polarization between close atoms in the same molecule, whose interactions

are instead described by valence terms.^{36,69} In PB calculations, electrostatic forces at the atomic sites can be subject to numerical instability because of the presence of point charges. Using the appropriate smoothing algorithms,⁵⁶ the calculated fields were only 10–30 times smaller than the self-fields, resulting in accurate results that agreed well with the other methods. We found that different dielectric boundary smoothing methods or grid spacings resulted in trivial changes (Tables S7 and S8, Supporting Information). In principle, the same equations (2)–(6) and reference state definition could be applied to calculating fields in a quantum mechanical model, but care would be needed to obtain a reliable difference between two large numbers with close values.

Another critical aspect of the electric field calculation was the choice to define the electric field *experienced* by the vibration in the simple manner expressed by eq 5. There is no unique way to define how a vibration senses its electrostatic environment, and many prescriptions (so-called frequency maps) have been developed;^{17,70–72} most are substantially more complex than eq 5. Our defense of eq 5 is based on its ability to produce values that correlate strongly with solvent-induced frequency shifts, its intuitive appeal, conceptual parsimony, and transferability across many different levels of theory. On that note, $\langle \vec{F}^C \cdot \hat{u}_{\text{CO}} \rangle$ and $\langle \vec{F}^O \cdot \hat{u}_{\text{CO}} \rangle$ by themselves had slightly worse power than $\langle |F_{\text{vib}}| \rangle$ to describe variation in C=O frequencies (based on t -values and R^2 's), and running a bivariate regression with those variables as independent explanatory variables gave an identical R^2 as the regression using just $\langle |F_{\text{vib}}| \rangle$ as the explanatory variable. Therefore, we believe $\langle |F_{\text{vib}}| \rangle$ is a simple and sufficient descriptor of the environment's electrostatic state, at least so far as the C=O frequency of acetophenone is concerned, and likely for the C=O frequency of other carbonyl-containing molecules as well.

4.5. Comments on Electric Field Scale. The calculations presented shed light on what is the overall scale of electric field that a polar solute experiences in liquid solutions. The three models employed (Poisson–Boltzmann, fixed-charge force field, AMOEBA force field) qualitatively agree it is on the order of 10–100 MV/cm, and that the change in field between a polar and nonpolar solvent, $|F_{\text{DMSO}}| - |F_{\text{hexane}}|$, is about $-30 \text{ MV}/\text{cm}$. On the other hand, acetophenone's frequency shift between these two solvents is 14.4 cm^{-1} and when combined with the measured Stark tuning rate of acetophenone, $|\Delta\bar{\nu}_{\text{C=O}}|/f$, of $1.05 \text{ cm}^{-1}/(\text{MV}/\text{cm})$,²³ one would predict the quantity $|F_{\text{DMSO}}| - |F_{\text{hexane}}|$ to be $-14 \text{ MV}/\text{cm}$. The scale of solvent electric fields predicted by models is therefore about twice as large as that suggested from the experimental solvent-induced frequency shifts and Stark tuning rate. This discrepancy has been observed in a few recent contributions;^{23,73} however, it has apparently gone largely unnoticed in prior literature, likely because correlations between model and observation were too weak for the models to make quantitative claims about the electric fields' absolute scale, and because of the practice of introducing post hoc dielectric rescaling factors.^{6,11,14,22,35,74} The present work presents two new models of solvent fields (AMOEBA and PB) in addition to the fixed-charge simulations previously reported,²³ which, in combination with the solvent-induced frequency shifts, corroborate an estimate of ca. $0.5 \text{ cm}^{-1}/(\text{MV}/\text{cm})$ for the effective tuning rate of the C=O vibration of acetophenone in liquid solution. Because this value is 2-fold smaller than the measured difference dipole of acetophenone from Stark spectroscopy,²³ we here consider potential systematic reasons for why the

effective Stark tuning rate in liquid solution could be different from what is measured in solid solution in vibrational Stark spectroscopy.

One key consideration is the local field effect, which modulates electric fields applied through an external voltage but does *not* affect the environment field (also known as the internal field in earlier literature) created by solvent molecules. When an external field is applied to a sample (as in a Stark experiment), the *local* field on a C=O probe due to the external charges will differ from the accurately known external (Maxwell) field by a factor called the local field correction factor (f).^{18,75} The local field will generally be larger because of extra contributions arising from polarization of the medium surrounding the C=O probe induced by the external field. The extent to which the local field is greater than the external field is not precisely known, and so experimental Stark tuning rates are reported as $|\Delta\vec{\mu}_{\text{C=O}}|f$, a product between the microscopic Stark tuning rate, $|\Delta\vec{\mu}_{\text{C=O}}|$, and the local field correction factor.

f has traditionally been estimated to be between 1.1 and 1.4 for frozen organic glasses^{18,68} (the environment in which Stark spectroscopy is typically carried out) on the basis of classic formulations from continuum dielectric theory. We found, however, that standard treatments omit important aspects of the local field effect, and that a more likely range for f is between 1.4 and 1.8 (see the Supporting Information discussion for derivation), implying that the microscopic Stark tuning rate for acetophenone, $|\Delta\vec{\mu}_{\text{C=O}}|$, is estimated to be between 0.58 and 0.75 $\text{cm}^{-1}/(\text{MV}/\text{cm})$, a range also in agreement with *ab initio* DFT calculations (Figure S3, Supporting Information). It deserves mention that models for the local field effect based on continuum dielectric theory make assumptions that are not appropriate for microscopic properties,¹⁸ and polarizable force fields may provide a means to make progress on describing the local field effect microscopically.⁷⁵

A second consideration is the fact that the difference dipole of a vibration comprises both an intrinsic portion arising from anharmonicity,^{14,19} $\Delta\vec{\mu}_{\text{M}}$ (present when the vibrational chromophore is in the gas phase), and an induced portion, $\Delta\vec{\mu}_{\text{ind}}$, arising from the interaction between the environment's electric field and the vibration's difference polarizability.⁷⁶ The induced portion of the difference dipole in a given environment will be reflected differently in the Stark and solvatochromism experiments. The induced difference dipole caused by an environment will be observed in full measure when a small external field supplements the field furnished by the environment, as in Stark spectroscopy. On the other hand, a frequency shift caused by a solvent field does not reflect the whole induced difference dipole present in the environment field, but rather, only half of it, because $\Delta\vec{\mu}_{\text{ind}}$ was itself due to the environment field that induced it. This is expressed mathematically as an alteration of eq 1 to

$$\bar{\nu}_{\text{obs}} - \bar{\nu}_0 = -\vec{F} \cdot \left(\Delta\vec{\mu}_{\text{M}}^{\text{probe}} + \frac{1}{2} \Delta\vec{\mu}_{\text{ind}}^{\text{probe}} \right) \quad (9)$$

On the other hand, in Stark spectroscopy, the difference dipole detected includes $\Delta\vec{\mu}_{\text{ind}}$ without the attenuating factor of one-half. This difference could make the tuning rate in a Stark experiment somewhat higher if the environment field in the Stark experiment is large enough to make the induced difference dipole significant (Figure S3, Supporting Information).⁷⁶ Although the difference polarizability is generally found to be small for vibrational transitions,^{14,19–23} the electric fields in solid solutions can be very large because of increased solvent

organization.⁷⁷ High level *ab initio* frequency calculations on polar diatomic molecules have shown that at larger electric fields, the quadratic contribution to frequency shifts (and by extension, the induced contribution to the difference dipole) is non-negligible.⁷⁸

Our current hypothesis is that a combination of the local field effect and the induced difference dipole explain the ca. 2-fold disagreement between the effective tuning rate from solvent-induced frequency shifts and the difference dipole measured in Stark spectroscopy. Needless to say, these hypotheses must be independently tested, as other unexplored sources of discrepancy are also possible. In particular, one previous study that focused on the O–H vibration of phenol in complex with various H-bond acceptors found that no local field correction was necessary to bring to accord the slope of the field-frequency curve and the Stark tuning rate.⁷⁹ A careful retrospective is necessary (and underway) to comprehend electric field calculations and vibrational Stark effects into a unified paradigm.

A critical consequence that follows from this discussion is that the electric fields in the condensed phase are larger than what would be estimated from vibrational frequency measurements coupled with the observed Stark tuning rate. In particular, the electric field acetophenone's C=O moiety experiences in water would be quite large (ca. 70 MV/cm). The presence of water on the same linear regression line (Figure 1A) implies that the C=O vibration maintains linear sensitivity to the electric field out to fields as high as 70 MV/cm.¹² For perspective, an electric field of this magnitude would impose an energetic penalty of $\sim 6.7 \text{ kcal mol}^{-1}$ on a point dipole of 1 D to reverse its orientation. To connect this number to experiment, in the classic aqueous ferrous–ferric self-exchange reaction, the outer-sphere reorganization energy involves the effective reversal of a dipole consisting of $\pm 0.5e$ displaced over the diameter of an iron atom.^{62,80} Modeling iron's van der Waals radius at 2 Å, the magnitude of the dipole to be reversed is $\sim 9.6 \text{ D}$, implying a reorganization energy of 64 kcal mol^{-1} . The experimental reorganization energy based on Marcus theory is 67 kcal mol^{-1} .⁸⁰ This short calculation illustrates that the large electric fields reported in Table 1 have some physical basis, though more systematic tests are still needed.

5. CONCLUDING REMARKS

The notion that solvent-induced spectral shifts are related to the Stark effect is an old one.^{30,31} With the help of polarizable force fields, we have extended that reductionist concept and posit that solvent effects, hydrogen bonding, and condensed-phase effects can all be quantitatively interpreted as electric field (Stark) effects. The task falls mostly to using a model of sufficient sophistication to calculate the average electric field in the environment of interest. To reiterate, only polarizable models (e.g., AMOEBA and PB) can account for the condensed-phase shift (gas phase to *n*-hexane), an atomistic model (e.g., AMOEBA and fixed-charge) is necessary to account for H-bonding shifts (DMSO to water), and all three categories of models can account for shifts associated with solvent polarity (*n*-hexane to DMSO). Therefore, AMOEBA was the only model examined that could properly describe nonpolar environments and highly polar H-bonding environments consistently. Polarizable force fields such as AMOEBA are uniquely suited for this task, because two major components that are needed to describe the electric field in the condensed phase accurately are polarization and sampling.

Polarization is missing in fixed-charge models, and sampling is unwieldy in ab initio treatments. We found that fixed-charge force fields can recapitulate certain aspects of the polarizable model, but they are less adept at describing interactions between polar and nonpolar entities,⁶⁶ which would seem to be critical when proteins are simulated. Drawing analogies to solvation phenomena has been useful in the past for developing models and interpreting data on protein structure and dynamics. We believe that vibrational frequency shifts lend themselves well to an interpretation that is transferable between solvents and proteins, and that they will continue to lead to physical insights on the organized environments of proteins and how functional properties emerge from them.

■ ASSOCIATED CONTENT

■ Supporting Information

Electric field trajectories and histograms, full electric field data tables, PB controls with alternative settings, modifications to TINKER source code and Python scripts needed for calculating electric fields with AMOEBA, discussion on the local field correction, and AMOEBA parameters for all molecules simulated. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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Supplementary Information

for

Calculations of the Electric Fields in Liquid SolutionsStephen D. Fried¹, Lee-Ping Wang¹, Steven G. Boxer¹, Pengyu Ren², Vijay S. Pande^{1*}¹ Department of Chemistry, Stanford University; Stanford, California² Department of Biomedical Engineering, University of Texas; Austin, Texas

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I. Supplementary Figures

Figure S1: Sample electric field trajectories

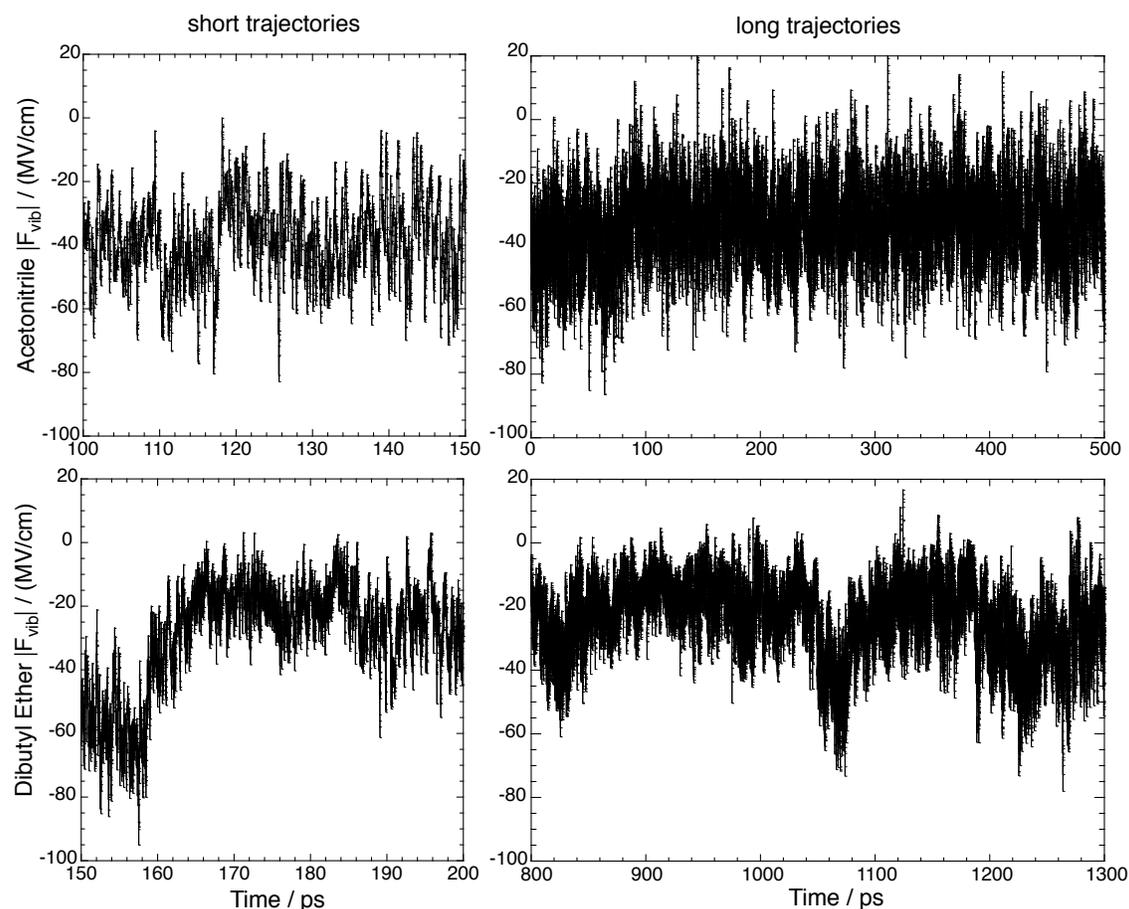


Figure S1. Segments of the electric field trajectories for long (right side) and short (left side) simulations of acetonitrile (top half) and dibutyl ether (bottom half). 50-ps segments were selected from the short trajectory and 500-ps segments from the long trajectories.

Inspection of acetonitrile's trajectories (top) shows that the electric field displays slight memory on the picosecond timescale, but little memory on the tens or hundreds of picoseconds timescales, in agreement with the time constants from the autocorrelation functions. Acetonitrile's field trajectory is representative of all the other solvents studied, except for dibutyl ether (bottom), which alone displayed slow dynamics on the tens (or even hundreds) of picoseconds timescales.

The 50-ps segment (bottom left) shows a close-up of one of the slow process, of which there are a number examples in the 500-ps segment. These types of dynamics imply

that dibutyl ether would require longer equilibration in order to reach the equilibrium ensemble, and longer production dynamics to converge ensemble-average properties.

Figure S2: Sample electric field histograms

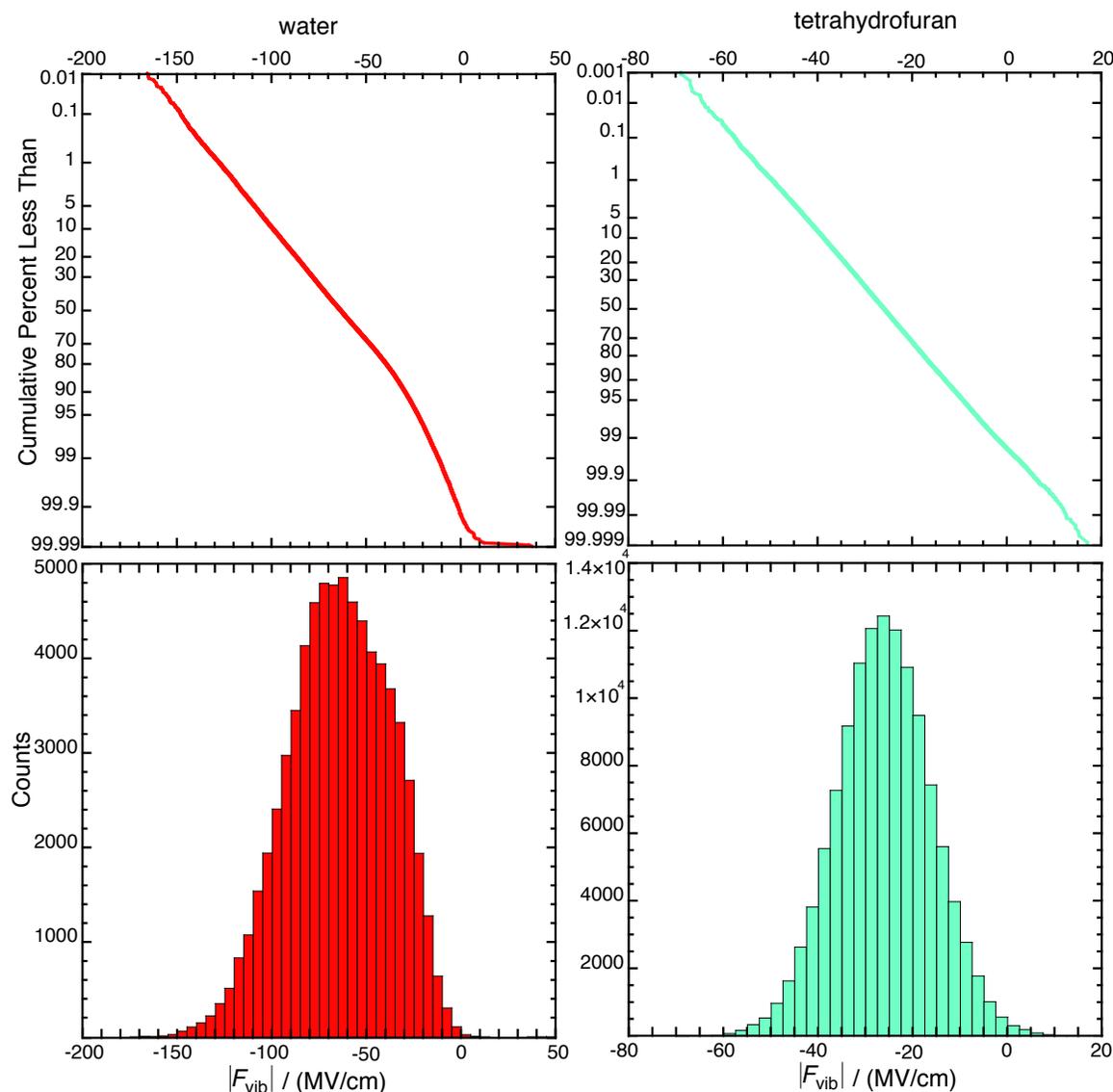


Figure S2. Electric field histograms (bottom half) and cumulative distribution functions (top half) for the long simulations of water (left side) and tetrahydrofuran (right side). The vertical axis of the histograms use a linear scale to illustrate the preponderance of the probability mass, whereas the cumulative distribution functions use a logarithmic scale to illustrate how far out the tails extend.

Tetrahydrofuran is representative of most of the solvents examined. Its electric field distribution is described almost perfectly by the normal distribution. The electric field is positive (the overall interaction between the solvent and C=O is unfavorable) about 1% of the time.

Water's electric field distribution is different – it conforms to the normal distribution less strictly. The histogram shows a larger-than-expected tail on the negative end (to more favorable electric fields), and the positive end has a sharper drop-off. Non-normal

behavior is evinced clearly by the non-linearity in the log cumulative plot (top). Hexane was the only other solvent that displayed this skew to its distribution.

Due to water's skew toward negative electric fields, it very infrequently sampled electric fields greater than zero ($< 0.1\%$) and was capable of appreciably sampling electric fields more than twice its mean ($\sim 1\%$).

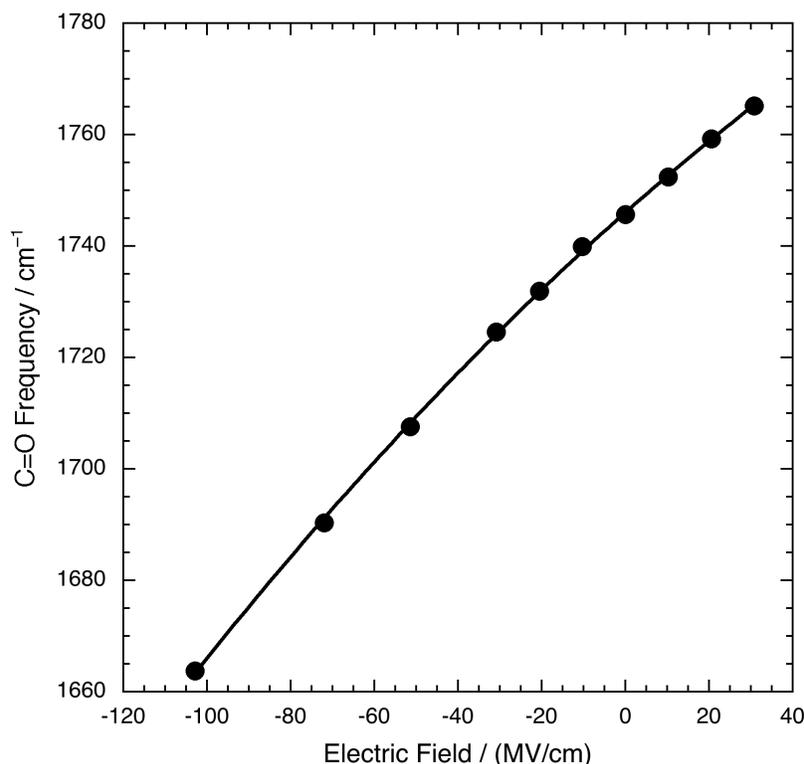
Figure S3: *Ab initio* field-frequency curve for acetophenone

Figure S3. The calculated harmonic frequency of the C=O stretch of acetophenone after being geometry optimized in the presence of a uniform electric field oriented along the C=O bond axis. Calculations were carried out by density functional theory at the B3LYP/6-311++G(d,p) level. The field-induced frequency shifts are well described by the model $\bar{\nu} = 1746 + 0.668F - 0.00133F^2$ with an R^2 of 0.9998.

The linear sensitivity term (corresponding to the difference dipole in $\text{cm}^{-1}/(\text{MV}/\text{cm})$) is within the estimated range for the microscopic Stark tuning rate ($0.58 - 0.75 \text{ cm}^{-1}/(\text{MV}/\text{cm})$) assuming a local field correction factor, $1.4 < f < 1.8$. The quadratic sensitivity term corresponds to one half the difference polarizability in $\text{cm}^{-1}/(\text{MV}/\text{cm})^2$.

Although the parabolic shape of the curve is slightly apparent at high electric fields, in the range of electric fields accessible to solvents (between -10 and $-70 \text{ MV}/\text{cm}$) the trend is essentially linear (a least squares regression line in this range has an R^2 of 0.999), consistent with the strong linear trends in Figure 1A from the main text. In Stark spectroscopy, small external fields are applied relative to the solid solution's environment field, implying the Stark tuning rate is well described by the derivative expression: $|\Delta\bar{\mu}| = d\bar{\nu}/dF = 0.668 - 0.00266F$, where the first term corresponds to $\Delta\bar{\mu}_M$ and the second to $\Delta\bar{\mu}_{ind}$ using the notation from the main text. At the large environment fields present in a cold organic glass (-50 to $-70 \text{ MV}/\text{cm}$), the induced term would contribute an additional 20–30 % of the intrinsic difference dipole to the total difference dipole.

II. Supplementary Tables

Table S1: Electric field data from the short trajectories^a

solvent		aceto- nitrile	DMSO	hexane	valero- nitrile	THF	water	dibutyl ether
n^b		24050	17184	18140	18159	15098	11069	10619
$ F^C ^c$	mean	-23.56 ± 0.69	-29.60 ± 1.13	-7.42 ± 0.27	-24.14 ± 0.71	-21.37 ± 0.81	-43.56 ± 1.18	-15.86 ± 1.57
	std.	10.82	11.36	3.42	9.45	9.21	17.82	8.88
$ F^O ^c$	mean	-48.66 ± 0.98	-56.10 ± 1.67	-14.40 ± 0.47	-47.31 ± 2.42	-39.90 ± 2.43	-95.44 ± 4.97	-32.46 ± 2.08
	std.	16.82	17.58	7.08	17.42	12.99	36.87	14.2
$ F_{vib} ^c$	mean	-36.11 ± 0.82	-42.85 ± 1.38	-10.91 ± 0.37	-35.73 ± 1.54	-30.63 ± 1.47	-69.5 ± 3.04	-24.16 ± 1.74
	std.	12.69	13.39	4.91	12.49	9.95	26.12	10.49
$ \Delta F_{vib} _c$	Mean	-25.1 ± 0.45	-26.49 ± 0.70	-6.98 ± 0.21	-23.16 ± 1.76	-18.53 ± 2.13	-51.88 ± 3.89	-16.60 ± 1.25
	std.	12.49	12.60	5.20	12.72	10.56	25.00	10.98

^a Some of these data also appeared in Table 1. They are reproduced here to ease comparisons. ^b The number of electric field data points recorded for this trajectory, each taken 10 fs after one another. ^c $|F^C|$ and $|F^O|$ are abbreviations for $\vec{F}^C \cdot \hat{u}_{CO}$ and $\vec{F}^O \cdot \hat{u}_{CO}$ respectively. $|F_{vib}|$ and $|\Delta F_{vib}|$ are the electric field experienced by the C=O vibration and the electric field drop along C=O respectively, as defined by Eq. 5 and Eq. 6 in methods section 2.4. All electric fields are in units of MV/cm.

Table S2: Electric field data from the long trajectories ^a

solvent		aceto- nitrile	DMSO	hexane	valero- nitrile	THF	water	dibutyl ether
n ^b		189489	136069	100767	98631	124246	69979	140186
$ F^C $ ^c	mean	-19.98 ± 0.34	-26.28 ± 0.37	-5.34 ± 0.19	-20.08 ± 0.35	-17.72 ± 0.39	-40.65 ± 1.57	-16.62 ± 0.81
	std.	9.97	10.60	3.44	9.88	9.23	17.77	8.98
$ F^O $ ^c	mean	-42.28 ± 0.45	-51.75 ± 0.56	-11.35 ± 0.28	-42.61 ± 0.85	-34.54 ± 0.69	-88.41 ± 2.82	-31.65 ± 1.39
	std.	16.38	15.86	6.87	17.93	12.92	37.66	14.85
$ F_{vib} $ ^c	mean	-31.13 ± 0.38	-39.02 ± 0.41	-8.34 ± 0.23	-31.35 ± 0.56	-26.13 ± 0.51	-64.53 ± 2.18	-24.13 ± 1.08
	std.	12.28	11.95	4.83	13.07	10.07	26.62	11.16
$ \Delta F_{vib} $ ^c	Mean	-22.30 ± 0.27	-25.47 ± 0.48	-6.01 ± 0.12	-22.53 ± 0.66	-16.82 ± 0.44	-47.76 ± 1.35	-15.03 ± 0.68
	std.	11.51	12.52	4.97	12.44	9.91	25.14	10.16

^a Electric fields from the longer trajectories, simulated with the settings described in methods section II.C. ^b The number of electric field data points recorded for this trajectory, each taken 10 fs after one another. ^c $|F^C|$ and $|F^O|$ are abbreviations for $\vec{F}^C \cdot \hat{u}_{CO}$ and $\vec{F}^O \cdot \hat{u}_{CO}$ respectively. $|F_{vib}|$ and $|\Delta F_{vib}|$ are the electric field experienced by the C=O vibration and the electric field drop along C=O respectively, as defined by Eq. 5 and Eq. 6 in methods section 2.4. All electric fields are in units of MV/cm.

The following tables present electric fields calculated by solving the PB equation with different dielectric constants than that used in the main text (Table 2). Using the conventions in APBS, 'pdie' refers to the internal dielectric of the solute, and 'sdie' refers to the external dielectric of the solvent continuum. 'sys' refers to the calculation in which sdie is set equal to the static dielectric constant of the solvent under consideration, and 'ref' refers to the reference calculation designed to represent the solute in the gas phase. Note that the setting in the main text is pdie(sys) = 2, pdie(ref) = 2, and sdie(ref) = 1.

Table S3: Electric fields calculated by solving PB with pdie(sys) = 1, pdie(ref) = 1, and sdie(ref) = 1^a

Solvent (static dielectric)	$ F_{vib} $ / (MV/cm)	$ \Delta F_{vib} $ / (MV/cm)
Hexane (1.78)	-14.88	-0.02
Dibutyl Ether (3.08)	-25.33	0.66
Tetrahydrofuran (7.43)	-36.13	2.49
Valeronitrile (20.04)	-42.69	5.03
Acetonitrile (37.50)	-45.32	6.42
Dimethyl Sulfoxide (46.84)	-46.16	6.73
Water (78.54)	-48.15	6.79

^a Solvent fields in which the internal dielectric is set to 1. While this setting produces an estimate for water's electric field that is closer to that of the all-atom models (which is perhaps why it was recommended by Swanson et al.), the electric fields are on the whole too large, leading to a field-frequency slope of 0.329 cm⁻¹/(MV/cm) and overall worse agreement with the all-atom models.

Table S4: Electric fields calculated by solving PB with pdie(sys) = 2, pdie(ref) = 2, and sdie(ref) = 2^a

Solvent (static dielectric)	$ F_{vib} $ / (MV/cm)	$ \Delta F_{vib} $ / (MV/cm)
Hexane (1.78)	1.76	0.08
Dibutyl Ether (3.08)	-5.77	-0.06
Tetrahydrofuran (7.43)	-14.09	0.50
Valeronitrile (20.04)	-19.28	1.61
Acetonitrile (37.50)	-21.18	2.43
Dimethyl Sulfoxide (46.84)	-21.70	2.71
Water (78.54)	-22.75	3.25

^a Solvent fields in which the reference calculation is carried out on a homogeneous dielectric (as per custom) with pdie = sdie = 2. This setting produces the same *relative* fields as the setting in the main text, but in absolute terms, the fields are all shifted up by ca. 12 MV/cm. As hexane is assigned a positive (unfavorable) solvation field, this reference state is clearly unphysical.

The following tables present electric fields calculated by solving the PB equation with a different charge assignment for the solute than that used in the main text (Table 2). To ease comparisons, we kept the dielectric settings ($\text{pdie}(\text{sys}) = 2$, $\text{pdie}(\text{ref}) = 2$, $\text{sdie}(\text{ref}) = 1$) and the radius parameters (ref. 54 from main text) the same.

Table S5: Electric fields calculated by solving PB with CHELPG charges^a

Solvent (static dielectric)	$ F_{vib} / (\text{MV}/\text{cm})^b$	$ \Delta F_{vib} / (\text{MV}/\text{cm})^c$
Hexane (1.78)	-8.30	-2.80
Dibutyl Ether (3.08)	-14.64	-4.53
Tetrahydrofuran (7.43)	-21.71	-5.97
Valeronitrile (20.04)	-26.39	-6.73
Acetonitrile (37.50)	-28.27	-7.11
Dimethyl Sulfoxide (46.84)	-28.80	-7.23
Water (78.54)	-29.85	-7.51

^a The charges for acetophenone were obtained by optimizing acetophenone by DFT at the B3LYP/6-311+G(d,p) level, and utilizing the CHELPG population scheme of Breneman and Wiberg. ^b The electric fields are overall 15% smaller, which is consistent with the charges' magnitudes being 6–72% smaller than GAFF (36% on average). The fact that GAFF charges give results that agree better with MD attests to the importance of weighting polarization effects into the charges. ^c The electric field drops are significantly different from those found with GAFF charges, which were all close to zero. This demonstrates that GAFF charges produce unusually smooth reaction fields, which is not intrinsic to PB methods in general.

Table S6: Electric fields calculated by solving PB with PCM/CHELPG charges^a

Solvent (static dielectric)	$ F_{vib} / (\text{MV}/\text{cm})^b$	$ \Delta F_{vib} / (\text{MV}/\text{cm})^c$
Hexane (1.78)	-15.63	-23.39
Dibutyl Ether (3.08)	-27.24	-38.33
Tetrahydrofuran (7.43)	-41.46	-55.58
Valeronitrile (20.04)	-50.58	-66.35
Acetonitrile (37.50)	-53.36	-68.28
Dimethyl Sulfoxide (46.84)	-54.30	-69.21
Water (78.54)	-55.92	-70.53

^a The charges were assigned in a way designed to reflect self-polarization effects. For each solvent, solvent-induced CHELPG charges were obtained by running a DFT optimization in the presence of a PCM with a dielectric constant equal to that of the solvent. The charges put into the PB model were the gas-phase CHELPG charges (from above) plus one half the polarization charge for each atom, defined as the difference between the gas-phase charge and the PCM charge for that atom. During the reference calculation, the gas-phase CHELPG charges were used. ^b Including explicit solute polarization results in larger fields, resulting in better agreement for water, but worse overall agreement. ^c The large field drops suggest that artifacts may result from not conserving the solute charges in the reference state.

Table S7: Electric fields calculated by solving PB with a cubic-spline smoothed dielectric boundary^a

Solvent (static dielectric)	$ F_{vib} / (\text{MV/cm})$	$ \Delta F_{vib} / (\text{MV/cm})$
Hexane (1.78)	-9.78	-0.92
Dibutyl Ether (3.08)	-17.37	-1.05
Tetrahydrofuran (7.43)	-26.09	-0.50
Valeronitrile (20.04)	-32.12	0.13
Acetonitrile (37.50)	-34.78	0.06
Dimethyl Sulfoxide (46.84)	-35.60	-0.08
Water (78.54)	-37.32	-0.65

^a Dielectric settings are $\text{pdie}(\text{sys}) = 2$, $\text{pdie}(\text{ref}) = 2$, $\text{sdie}(\text{ref}) = 1$, same as the main text. The only difference is the method for smoothing the dielectric boundary (srfm) is set to be the same as that used by Swanson et al. For the electric fields, the difference is negligible; however, the cubic-spline smoothed boundary produces electric field drops that are closer to zero.

Table S8: Electric fields calculated by solving PB with 0.1 Å grid spacings^a

Solvent (static dielectric)	$ F_{vib} / (\text{MV/cm})$	$ \Delta F_{vib} / (\text{MV/cm})$
Hexane (1.78)	-9.87	-0.93
Dibutyl Ether (3.08)	-17.39	-1.04
Tetrahydrofuran (7.43)	-25.75	-0.55
Valeronitrile (20.04)	-31.21	0.04
Acetonitrile (37.50)	-33.33	0.29
Dimethyl Sulfoxide (46.84)	-33.92	0.35
Water (78.54)	-35.05	0.49

^a Dielectric settings are $\text{pdie}(\text{sys}) = 2$, $\text{pdie}(\text{ref}) = 2$, $\text{sdie}(\text{ref}) = 1$, same as the main text. The only difference is finer grid spacings are used.

III. Supplementary Methods

The following sections are designed to help readers carry out electric field calculations in TINKER according to the methods section 2.4 from the main text. To understand conceptually what is going on, please refer to the main text; the following sections are focused on walking through the implementation.

Some initial notes:

1. The following source code modifications were made on TINKER version 6.2, available online at <http://dasher.wustl.edu/ffe/>, and released in February 2013. Although it is probable the same modifications will work on future versions of TINKER, we cannot predict the future.
2. The electric field calculations described in the following are designed to be used in conjunction with a polarizable force field using a site-based point inducible dipole model (such as AMOEBA). Otherwise, the methods described below will not work.
3. The modified TINKER source code is also available online at http://www.stanford.edu/~sdfried/take-aways/tinker-2_src.tar.gz

1. Modifications to and compilation of TINKER.

Download the TINKER source code from `dasher` as a GNU zip, and un-tar. `cd` into the `source` directory. Here you will find a large number of files ending in `.f` – these are FORTRAN 95 programs. At this point, either make the following changes to the source code by hand (*vide infra*), OR `rm` the `source` directory and replace it with the one available from my website, which has the modified source code files. This modified version of TINKER is later referred to as `tinker-2`. The changes are each given a brief explanation.

- (1) **dynamic.f** – electric field calculations require the ability to evaluate the induced dipoles on atoms of interest for particular configurations without running dynamics. We introduce the 0-time-step flag to indicate this option. These induced dipole evaluations are done snapshot-by-snapshot, and therefore automation is handled at the scripting level. Setting `nstep` to 0, calls `verlet`, supplying it with `istep = 0` (the flag for the further subroutines), and an infinitesimally small time-step (10 attoseconds).

```

10 continue
   if (query) then
       write (iout,20)
20   format (/, ' Enter the Number of Dynamics Steps to be',
   &      ' Taken (0 to perform single-pt rerun): ', $)
       read (input,30) nstep
30   format (i10)

```

```

c
c   flag to perform a single-point force evaluation of a given input
c   snapshot (added by SDF)
c

```

```

        if (nstep .eq. 0) goto 500
    end if

...

c
c   perform a single-pt force evaluation (added by SDF)
c
500 continue
    call verlet (0,0.001d0)

c
c   perform any final tasks before program exit
c
510 continue
    call final
    end

```

- (2) **verlet.f** – verlet proceeds as usual, altering coordinates infinitesimally from the snapshot, calls mdsave, and then quits. Skipping Verlet recursion entirely (as opposed to performing it with an infinitesimal time-step) appeared to produce artifacts.

```

c
c   store the current atom positions, then find half-step
c   velocities and full-step positions via Verlet recursion
c
do i = 1, n
    if (use(i)) then
        do j = 1, 3
            v(j,i) = v(j,i) + a(j,i)*dt_2
        end do
        xold(i) = x(i)
        yold(i) = y(i)
        zold(i) = z(i)

c
c   THIS ONLY HAPPENS IF ISTEP NEQ 0 (added by SDF)
c
        if (istep .ne. 0) then
            x(i) = x(i) + v(1,i)*dt
            y(i) = y(i) + v(2,i)*dt
            z(i) = z(i) + v(3,i)*dt
        end if

        end if
    end do

...

c
c   if performing a single-pt force evaluation, skip over mdstat and
c   mdrest (added by SDF)
c
    if (istep .eq. 0) then

```

```

        call mdsave (istep,dt,epot)
        goto 500
    end if
c
c   compute statistics and save trajectory for this step
c
    call mdstat (istep,dt,etot,epot,eksum,temp,pres)
    call mdsave (istep,dt,epot)
    call mdrest (istep)
500 continue
    return
    end

```

- (3) **mdsave.f** – at the beginning, mdsave checks to see if we are performing a single-point induced dipole evaluation. If so, it immediately runs the code that would *normally* be run if the save-induced option were included in the key file. The format has been altered so that higher floating-point precision is recorded.

```

c
c
c   send data via external socket communication if desired
c
    if (.not.skt_init .or. use_socket) call sktdyn (istep,dt,epot)
c
c   if performing a single-pt induced dipole evaluation, output high-
c   precision dipoles and quit (added by SDF)
c
    if (istep .eq. 0) then
        iind = freeunit ()
        indfile = filename(1:leng)//'.u'
        call version (indfile,'new')
        open (unit=iind,file=indfile,status='new')
        write (iind,540) n,title(1:ltitle)
540    format (i6,2x,a)
        do i = 1, npole
            if (polarity(i) .ne. 0.0d0) then
                k = ipole(i)
                write (iind,550) k,name(k),(debye*uind(j,i),j=1,3)
c 550    format (i6,2x,a3,3f12.6)
550    format (i6,2x,a3,3f18.12)
            end if
        end do
        close (unit=iind)
        goto 560
    end if
...
560 continue
    return
    end

```

- (4) **archive.f** – the archive program is invoked a number of times in the electric field calculations in order to extract snapshots from archives (as noted in (1) the re-run is done one snapshot at a time) and to automate the creation of the solute-only

reference trajectory. In particular, the latter task involves executing `archive` with the `trim` option. Natively, `trim` is designed to remove only a few atoms, so a few variables must be altered so that `trim` can remove 1000's of atoms (i.e., the whole solvent).

```

integer freeunit
integer list(20000)
real*8 xr,yr,zr
...
character*120 record
character*100000 trimrecord
character*120 string
...
c
c decide whether atoms are to be removed from each frame
c
  if (modtyp .eq. 'TRIM') then
    call active
    if (nuse .eq. n) then
      do i = 1, 20000
...
140     format (/, ' Numbers of the Atoms to be Removed : ', $)
        read (input,150) trimrecord
150     format (a100000)
        read (trimrecord,*,err=160,end=160) (list(i),i=1,20000)
160     continue

```

For installation, we used the `intel-13` FORTRAN compilers configured for the linux architecture. Using a bash command line, `cp` the `.make` files from `/linux/intel` into `/source`. You will also need to acquire the relevant FFTW3 libraries for your system's architecture and make sure they are in the `/source` directory as well. If all goes well, it should be as simple as:

```

./compile.make
./library.make
./link.make
mkdir ../bin
./rename.make

```

2. Settings for running production runs

A typical production run would be initiated with files with names such as `acp_hex_md.xyz` and `acp_hex_md.key`, where the naming convention goes `solute_solvent_md.fileType`. The naming convention is not of paramount importance, but should be maintained if the reader desires to use the electric field calculation script as is without modification.

The file `solute_solvent_md.xyz` is a standard `xyz` starting coordinates file, except the solute molecule must come first before the entries corresponding to solvent atoms.

The file `solute_solvent_md.key` defines the functional form of the force field, simulation control settings, and (in our case) all the force field parameters as well. The control settings were as follows:

```
# Electrostatics and vdW
ewald
vdw-correction
ewald-cutoff          10.0
vdw-cutoff            10.0
polar-eps             0.00001

# Dynamics
integrator            beeman
thermostat            bussi
barostat              montecarlo
friction              1.0
volume-scale          molecular

# Output
archive
openmp-threads        8
mpole-list
save-induced
```

where the options in red are essential.

3. Python script to calculate electric fields

```
#!/usr/bin/env python
#This is a script that obtains the electric fields from a TINKER
trajectory
#stored in the format of an arc file. Created by SDF 20121030.

#Prerequisites:
# -1- A flat-text trajectory with fn format solute_solvent.arc (no
numbers)
# -2- A key file with the same base filename as the arc file
# -3- A flat-text uind file

#Call the script as:
# python get_fields.py system.arc system.key system.uind

import sys
import re
import numpy as np
import os

def create_perturbed_key(old_kn, new_kn, dq, delbox=False):
    old_key = open(old_kn)
    new_key = open(new_kn, 'w')
    omp_flag = False
    for line in old_key:
        if delbox and 'a-axis' in line: continue
        if delbox and 'b-axis' in line: continue
        if delbox and 'c-axis' in line: continue
        if re.search(r'multipole\s+%s' %(atomTypeC), line) or
re.search(r'multipole\s+%s' %(atomTypeO), line):
            atomInfo = line.split()
            whitespace = re.split(r'\S+', line)
            newline = ''
            atomInfo[-1] = str( float(atomInfo[-1]) + dq)
            for i in range( len(atomInfo) ):
                newline += whitespace[i]
                newline += atomInfo[i]
            newline += '\n'
            new_key.write( newline )
        else:
            new_key.write( line )
            if "openmp-threads" in line:
                new_key.write("openmp-threads 1")
                omp_flag = True
    if not omp_flag:
        new_key.write("openmp-threads 1")
    new_key.close()
    old_key.close()

def getInfo(arc_fn):
    solute = arc_fn.split('.')[0].split('_')[0]
    solvent = arc_fn.split('.')[0].split('_')[1]
    return solute, solvent

def getSystemInfo(arc_fn):
    arc_file = open( arc_fn, 'r' )
    first_line = arc_file.next()
```

```

numAtoms = int( first_line.split()[0] )
numLines = sum(1 for line in arc_file)
numSnapshots = (numLines/numAtoms)
arc_file.close()
return numSnapshots, numAtoms

def getSoluteInfo(solute):
    if solute == 'acp':
        return 17, 5, 6
    else:
        print "How many solute atoms are there?"
        numSoluteAtoms = raw_input()
        print "What is the index of the C atom?"
        indexC = raw_input()
        print "What is the index of the O atom?"
        indexO = raw_input()
        return int(numSoluteAtoms), int(indexC), int(indexO)

def getAtomTypes(solute_fn):
    solute_file = open( solute_fn, 'r')
    for line in solute_file:
        infoInLine = line.split()
        if len(infoInLine) >= 6:
            if infoInLine[0] == str(indexC):
                atomTypeC = infoInLine[5]
            if infoInLine[0] == str(indexO):
                atomTypeO = infoInLine[5]
    solute_file.close()
    return atomTypeC, atomTypeO

def whichSnapshot(filename):
    ss = int( (re.search(r'\d+', filename)).group() )
    return ss

def convert(x):
    try:
        float(x)
        return float(x)
    except ValueError:
        mantissa = float( x.split('D')[0] )
        expo = int( x.split('D')[1] )
        return mantissa * 10**expo

#MAIN STARTS HERE
#Get the filenames from the command
arc_fn = sys.argv[1]
key_fn = sys.argv[2]
uind_fn = sys.argv[3]

#find out the identity of the solute and solvent
solute, solvent = getInfo(arc_fn)

#find out the number of snapshots and the number of atoms by peeking
into the arc file
numSnapshots, numAtoms = getSystemInfo(arc_fn)
numSoluteAtoms, indexC, indexO = getSoluteInfo(solute)

#create solute-only archive

```

```

trim = open('trim.in', 'w')
trim.write( '%s \n' %(arc_fn) )
trim.write( '3 \n' )
trim.write( ' '.join(str(n) for n in range(numSoluteAtoms+1,
numAtoms+1)) + '\n')
trim.write( '1 %d 1 \n' %(numSnapshots) )
trim.close()
command = 'cat trim.in | ~/Programs/tinker-2/bin/archive'
os.system(command)
os.rename('%s_2' %(arc_fn) , '%s.arc' %(solute) )

#extract solute-only snapshots, place in a temp dir
os.mkdir('%s_xyzs' %(solute))
os.chdir('./%s_xyzs' %(solute)) #go into solute_xyzs

extract = open('extract.in', 'w')
extract.write( '../%s.arc \n' %(solute) )
extract.write( '2 \n' )
extract.write( '1 %d 1 \n' %(numSnapshots) )
extract.close()
command = 'cat extract.in | ~/Programs/tinker-2/bin/archive'
os.system(command)
for fn in os.listdir('.'):
    if fn != 'extract.in':
        fn_new = fn.translate(None, '.') + '.xyz'
        os.rename(fn, fn_new)

#Get the atom-types for the probeC and probeO atoms
atomTypeC, atomTypeO = getAtomTypes( '%s001.xyz' %(solute) )

#Make a key file for the single-pt uind evaluations for the solute
solutekey_fn = '%s.key' %(solute)
create_perturbed_key('../%s' %(key_fn), solutekey_fn, 0, delbox=True)

#perform single-pt uind evaluations on the solute snapshots
for fn in os.listdir('.'):
    if fn.endswith('.xyz'):
        print "getting induced dipoles from %s" %(fn)
        command = '~/Programs/tinker-2/bin/dynamic %s %s 0' %
(fn,solutekey_fn)
        os.system(command)

#copy all of the data from files into an array
#rawData[i,j,k,l] stores
    #for the i^th snapshot (0 to numSnapshots-1)
    #for the j^th atom (C=0, O=1)
    #for the k^th component (x=0, y=1, z=2)
    # the l^th information (coord=0, uindTot=1, uindRef=2)
rawData = np.zeros( (numSnapshots, 2, 3, 3) )

#we're still in solute_xyzs
for fn in os.listdir('.'): #loop thru all files in this directory,
    garnering the relevant data
    if fn.endswith('.xyz'): #if an xyz file, grab coordinates, l=0
        ss = whichSnapshot( fn )
        xyz = open( fn , 'r')
        for line in xyz:

```

```

        infoInLine = line.split()
        if len(infoInLine) >= 6:
            if infoInLine[0] == str(indexC):
                rawData[ss-1,0,0:3,0] = [convert(x) for x in
infoInLine[2:5]]
            if infoInLine[0] == str(indexO):
                rawData[ss-1,1,0:3,0] = [convert(x) for x in
infoInLine[2:5]]
            xyz.close()
        elif fn.endswith('.u'): #if an u file, grab reference induced
dipoles, l=2
            ss = whichSnapshot( fn )
            u = open( fn , 'r')
            for line in u:
                infoInLine = line.split()
                if len(infoInLine) >= 5:
                    if infoInLine[0] == str(indexC):
                        rawData[ss-1,0,0:3,2] = [convert(x) for x in
infoInLine[2:5]]
                    if infoInLine[0] == str(indexO):
                        rawData[ss-1,1,0:3,2] = [convert(x) for x in
infoInLine[2:5]]
                u.close()
            else:
                pass

#now go into the original uind archive file
os.chdir('..')
uind = open( uind_fn , 'r')
ss = 0
for line in uind:
    infoInLine = line.split()
    if len(infoInLine) < 5:
        ss += 1
    else:
        if infoInLine[0] == str(indexC):
            rawData[ss-1,0,0:3,1] = [convert(x) for x in
infoInLine[2:5]]
        if infoInLine[0] == str(indexO):
            rawData[ss-1,1,0:3,1] = [convert(x) for x in
infoInLine[2:5]]
uind.close()

#now we are going to process rawData into procData
#procData[i,j,k,l] stores
    #for the i^th snapshot (0 to numSnapshots-1)
    #for the j^th atom (C=0, O=1)
    #for the k^th component (x=0, y=1, z=2)
    # the l^th information (field)
polarizaC = 1.3340
polarizaO = 0.8370
procData = np.zeros( (numSnapshots, 2, 3, 1) )
procData[:,0,:,0] = ((rawData[:,0,:,1] - rawData[:,0,:,2])) * 0.2082 *
1439 / polarizaC
procData[:,1,:,0] = ((rawData[:,1,:,1] - rawData[:,1,:,2])) * 0.2082 *
1439 / polarizaO

```

```

#now we are going to finalize procData into finalData
#finalData[i,j] stores
    #for the i^th snapshot (0 to numSnapshots-1)
    # the j^th field (field@C=0, field@O=1, fieldAve=2, fieldDrop=3)
finalData = np.zeros( (numSnapshots, 4) )

for i in range(numSnapshots): #for each snapshot
    #get the C & O coordinates
    #calculate the CO bond length and CO unit vector
    x_C = rawData[i,0,:,0]
    x_O = rawData[i,1,:,0]
    COvec = x_O - x_C
    COlen = np.linalg.norm( COvec )
    COunitvec = COvec / COlen

    #project the electric field onto the bond vector
    field_C = procData[i,0,:,0]
    field_O = procData[i,1,:,0]
    fieldproj_C = np.dot( field_C , COunitvec )
    fieldproj_O = np.dot( field_O , COunitvec )

    #calculate the average field and field drop
    fieldproj_ave = (fieldproj_C + fieldproj_O)/2
    fieldproj_drop = (fieldproj_O - fieldproj_C)

    #fill into finalData
    finalData[i,:] = fieldproj_C, fieldproj_O, fieldproj_ave,
    fieldproj_drop

#save finalData to file
print rawData
print procData
print finalData
np.savetxt( '%s_%s_FIELDS.txt' %(solute,solvent) , finalData )
print "calculation of fields for %s_%s completed." %(solute,solvent)
print "Terminating normally."

```

IV. Supplementary Discussion on the local field correction

When an *external* (Maxwell) field, \vec{F}_{ext} , is applied to a dielectric material, the *local* field, \vec{F}_{loc} , at a given position inside the dielectric is not necessarily the same as \vec{F}_{ext} . The differences arise from the polarization of the dielectric by the field. A number of strategies have been devised to evaluate the local field factor, f , defined as

$$\vec{F}_{loc} = f \vec{F}_{ext} \quad (S1)$$

where f is formally a tensor-quantity and position-dependent, although it is generally assumed to be scalar and constant for isotropic systems.⁶⁸ The local field effect impinges on a large range of experiments in which external fields are applied to condensed phase systems; it is relevant to the present discussion on vibrational Stark spectroscopy, since f affects the absolute magnitude of the difference dipole, $|\Delta\vec{\mu}|$, which in turn affects the scale of the electric fields assigned to vibrational frequency shifts. Beginning with early work on photosynthetic pigments,⁸⁰ a tentative value of 1.2 was assigned to f by Lockhart and Boxer, and in general the range of 1.1–1.4 has been assumed in following work.¹⁸

In light of recent results, a brief review of the local field factor, its derivation, and evaluation is merited. The most common equation used to model the local field factor is given by the spherical cavity approximation⁶⁸

$$\vec{F}_{loc} = \left(\frac{3\varepsilon}{2\varepsilon + 1} \right) \vec{F}_{ext} \quad (S2)$$

where ε is the static dielectric constant (relative permittivity) of the prevailing medium. The spherical cavity approximation is a special case of a classic problem in electrostatic theory concerning a sphere of dielectric ε_2 embedded in a second medium (of dielectric constant ε) extending to infinity. When an external field is applied to this system, the electric field *inside* the sphere is $3\varepsilon/(2\varepsilon + \varepsilon_2)$ times the external field.⁶⁸ Eq. S2 follows from setting $\varepsilon_2 = 1$, which effectively makes the sphere a cavity. Note that if $\varepsilon_2 < \varepsilon$, the electric field inside the sphere will be larger than that in the prevailing medium.

To evaluate f from Eq. S2, one must choose a value for the dielectric constant for organic glasses, the medium in which Stark spectroscopy was obtained on acetophenone²³ as well as on many small molecules.^{14,18,19,21,22,78} A typical range that is suggested for this is 2–4.^{18,80} Organic glasses evince rich dielectric phenomena near their glass-transitions,⁸¹ such as sharp reduction of the dielectric constant at the freezing point and hysteresis upon thawing and re-vitrifying. Nevertheless, in the cold limit ($T \ll T_g$) most non-hydrogen-bonding organic glasses have a non-hysteretic dielectric constants between 2–4,⁸¹ and the value is generally higher (5–6) for glasses made of hydrogen bonding molecules such as glucose or glycerol.⁸² By combining the range $2 < \varepsilon_{glass} < 5$ with Eq. S2, one obtains $1.2 < f < 1.4$, the range that has been reported in most work by Boxer and coworkers.

The principal conceptual problem with the spherical cavity approximation for the local field correction is that it assumes the cavity is empty; i.e., it ignores the solute. When an external field is applied, Eq. S2 accounts for the additional field in the cavity due to the polarization of the dielectric environment around the cavity, but does not consider the additional field due to the polarization of the solute (inside the cavity). In this case, the

Lorentz local field approximation provides a different approach based on a hypothetical virtual cavity and the field induced by apparent charges on the boundary of the cavity.^{68,75}

$$\vec{F}_{loc} = \left(\frac{2 + \varepsilon}{3} \right) \vec{F}_{ext} \quad (S3)$$

For the same range of glass dielectric ($2 < \varepsilon_{\text{glass}} < 5$), with Eq. S3 we now obtain $1.3 < f < 2.3$, a much larger range. It has long been known however that the Lorentz local field is inappropriate when the system consists of polar molecules possessing permanent dipole moments⁸³; indeed, it was derived prior to Debye's pioneering work that demonstrated molecules could even possess permanent dipoles.

It is apparent then that a new equation for the local field correction is needed that both accounts for the presence of a solute in the cavity and applies to polar molecules; we shall derive an expression for such in the following. To begin, we consider a solute (which is modeled as a polarizable point-dipole with polarizability, α) in a spherical cavity (of radius, a) in a dielectric medium (with dielectric constant, ε). We take the approach that Onsager took¹ of breaking down the total field in the cavity, \vec{F} , into two components: the cavity field, \vec{F}_C , and the reaction field, \vec{R} :

$$\vec{F} = \vec{F}_C + \vec{R} \quad (S4)$$

The cavity field is the portion of the total field that is present even when there is no point-dipole (solute) present, but requires an external field (amplified as according to Eq. S2). The reaction field is the portion of the total field that is present even when no external field is applied, but requires the presence of a point-dipole. The reaction field is analogous to what was referred to as the solvent field in this paper, and it can be calculated according to Eq. 7 from the main text. It is important to point out that in a model where reaction fields are included, the *local* field must be carefully defined as the *difference* in the total electric field at a point upon applying an external field.⁷⁵

When an external field is turned on, \vec{F} will change in two ways. First, the cavity field will change from zero to $3\varepsilon/(2\varepsilon + 1) \times \vec{F}_{ext}$. Secondly, the reaction field will change because the solute is polarizable and also responds to the external field. Mathematically, this is:

$$\begin{aligned} \vec{F}_{loc} &= \Delta\vec{F} = \vec{F}_{ext \text{ field on}} - \vec{F}_{ext \text{ field off}} = \left(\vec{F}_C + \vec{R}_{ext \text{ field on}} \right) - \vec{R}_{ext \text{ field off}} \\ &= \vec{F}_C + \Delta\vec{R} \end{aligned} \quad (S5)$$

$\Delta\vec{R}$ can be evaluated according to the following:

$$\begin{aligned} \Delta\vec{R} &= \left(\frac{1}{a^3} \frac{2(\varepsilon - 1)}{2\varepsilon + 1} \right) (\text{dipole due to ext field}) \\ &= f \left(\alpha\vec{F}_C + \alpha\Delta\vec{R} \right) \end{aligned} \quad (S6)$$

The first factor is the Onsager factor¹ which when multiplied by a molecule's dipole gives the reaction field. It is traditionally abbreviated f ; note that it is not the same as the local field factor, f . The second factor is the total dipole moment induced by the external field, which depends on the molecule's polarizability, the cavity field, and also on the reaction field itself (which additionally induces the dipole moment). The permanent dipole does

not appear in Eq. S6, since we are only interested in the *change* in reaction field upon applying an external field. The self-consistent equation can be solved for $\Delta\vec{R}$ to give

$$\Delta\vec{R} = \vec{F}_c \left(\frac{f\alpha}{1-f\alpha} \right).$$

Inserting this result back into Eq. S5, we obtain:

$$\begin{aligned} \Delta\vec{F} &= \vec{F}_c + \Delta\vec{R} = \vec{F}_c \left(\frac{1}{1-f\alpha} \right) \\ &= \left(\frac{3\varepsilon}{2\varepsilon+1} \right) \vec{F}_{ext} \left(\frac{1}{1 - \frac{\alpha}{a^3} \frac{2(\varepsilon-1)}{2\varepsilon+1}} \right) \\ &= \left(\frac{3\varepsilon}{2\varepsilon+1 - 2\alpha(\varepsilon-1)/a^3} \right) \vec{F}_{ext} \end{aligned}$$

In the second line, we have inserted the expression for the cavity field in terms of the external field (Eq. S2) and the Onsager factor (Eq. S6). The quantity in parentheses on the final line corresponds to the local field factor. We can remove the microscopic parameters (polarizability and molecular volume) by invoking the Lorentz-Lorenz equation (which relates polarizability to refractive index) and Onsager's ansatz that molecular volume is trivially related to formula weight and density, to give the final result:

$$\vec{F}_{loc} = \left(\frac{3\varepsilon}{2\varepsilon+1 - 2 \left(\frac{n^2-1}{n^2+2} \right) (\varepsilon-1) / a^3} \right) \vec{F}_{ext} \quad (\text{S7})$$

where one must be careful to note that n is the refractive index of the solute. Using Eq. S7 with n for acetophenone and the same range of glass dielectric ($2 < \varepsilon_{\text{glass}} < 5$), we obtain $1.4 < f < 1.8$. This range is consistent with the span of values calculated for the diagonal components of the local field tensor of crystalline durene and naphthalene.⁸⁴

In summary, Eq. S7 provides an expression for the local field correction that accounts for a polarizable solute that can respond to an external field as well as the polar environment surrounding the solute. Moreover, the upper value allowed to f by Eq. S7 is quite close to that implied by the AMOEBA-calculated solvent fields. Nevertheless, Eq. S7 suffers from the same underlying assumptions of dielectric continuum theory, which neglect the microscopic structure of matter and local interactions.

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V. Parameters

5.1 Acetonitrile

atom	210	79	C	"Acetonitrile CN"	6	12.011	2
atom	211	80	N	"Acetonitrile CN"	7	14.007	1
atom	212	82	C	"Acetonitrile CH3"	6	12.011	4
atom	213	83	H	"Acetonitrile H3C"	1	1.008	1
vdw	79			3.8200	0.1010		
vdw	80			3.5800	0.1100		
vdw	82			3.8200	0.1010		
vdw	83			2.9100	0.0330	0.900	
bond	79	80		1195.00	1.1700		
bond	79	82		380.00	1.4570		
bond	82	83		390.00	1.0873		
angle	80	79	82	65.00	180.00		
angle	79	82	83	45.00	109.92		
angle	83	82	83	40.00	109.02		
strbnd	80	79	82	18.70	18.70		
strbnd	79	82	83	11.50	11.50		
torsion	80	79	82	83	0.000	0.0	1
0.0	3				0.000	180.0	2
					0.000		0.000
multipole	210	211	0		0.50893		
					0.00000	0.00000	0.00838
					0.04512		
					0.00000	0.04512	
					0.00000	0.00000	-0.09024
multipole	211	210	0		-0.64934		
					0.00000	0.00000	-0.41663
					0.40285		
					0.00000	0.40285	
					0.00000	0.00000	-0.80570
multipole	212	210	0		-0.16118		
					0.00000	0.00000	0.17034
					-0.03526		
					0.00000	-0.03526	
					0.00000	0.00000	0.07052
multipole	213	212	210		0.10053		
					0.00543	0.00000	-0.12249
					0.11906		
					0.00000	0.00913	
					0.02813	0.00000	-0.12819
polarize	210			1.3340	0.3900	211	212
polarize	211			1.0730	0.3900	210	
polarize	212			1.3340	0.3900	210	213
polarize	213			0.4960	0.3900	212	

torsion 0.0 3	27	29	29	29	0.854	0.0	1	-0.374	180.0	2	0.108
torsion 0.0 3	27	29	29	30	0.000	0.0	1	0.000	180.0	2	0.341
torsion 0.0 3	29	29	29	29	0.854	0.0	1	-0.374	180.0	2	0.108
torsion 0.0 3	29	29	29	30	0.000	0.0	1	0.000	180.0	2	0.108
torsion 0.0 3	30	29	29	30	0.000	0.0	1	0.000	180.0	2	0.299
torsion 0.0 3	40	36	40	44	0.000	0.0	1	0.000	180.0	2	0.597
torsion 0.0 3	36	40	40	40	-1.150	0.0	1	0.000	180.0	2	1.280
torsion 0.0 3	27	29	29	40	0.854	0.0	1	-0.374	180.0	2	0.108
torsion 0.0 3	29	29	40	44	0.000	0.0	1	0.000	180.0	2	0.108
torsion 0.0 3	29	29	40	36	-1.150	0.0	1	0.000	180.0	2	1.280
torsion 0.0 3	29	40	36	40	0.000	0.0	1	-0.837	180.0	2	3.204
torsion 0.0 3	30	29	29	40	0.000	0.0	1	0.000	180.0	2	0.108
torsion 0.0 3	30	29	40	44	0.000	0.0	1	0.000	180.0	2	0.340
torsion 0.0 3	30	29	40	36	0.000	0.0	1	0.000	180.0	2	0.300
multipole	29	31	30		-0.16638						
					0.00000			0.00000			0.25069
					-0.24574						
					0.00000			-0.24574			
multipole	30	29	31		0.00000			0.00000			0.49148
					0.05546						
					0.01102			0.00000			-0.10399
					0.00247						
					0.00000			-0.01906			
multipole	31	31	29		0.00852			0.00000			0.01659
					-0.12028						
					0.33700			0.00000			0.22666
					0.34191						
					0.00000			-0.72407			
multipole	31	-31	-31		-0.04985			0.00000			0.38216
					-0.12028						
					0.00000			0.00000			0.27522
					0.47728						
					0.00000			-0.35302			
multipole	32	31	31		0.00000			0.00000			-0.12426
					0.06014						
					0.00606			0.00000			-0.08554
					-0.00370						
					0.00000			-0.01833			
multipole	58	59	59		0.00546			0.00000			0.02203
					-0.32494						
					0.53657			0.00000			0.37202
					0.44076						

				0.00000	-0.87825	
				0.00127	0.00000	0.43749
multipole	59	58	59	0.11615		
				-0.19923	0.00000	0.19298
				-0.23681		
				0.00000	-0.41373	
				-0.10899	0.00000	0.65054
multipole	60	59	58	0.02316		
				0.04231	0.00000	-0.02407
				-0.01587		
				0.00000	-0.05904	
				0.03668	0.00000	0.07491
polarize	29		1.3340	0.3900	30	
polarize	30		0.4960	0.3900	29	
polarize	31		1.3340	0.3900	32	
polarize	32		0.4960	0.3900	31	
polarize	58		0.8370	0.3900	59	
polarize	59		1.3340	0.3900	58	60
polarize	60		0.4960	0.3900	59	

5.3. Dimethyl Sulfoxide

atom	189	72	S	"Dimethyl Sulfoxide S=O"	16	32.066	3
atom	190	73	O	"Dimethyl Sulfoxide S=O"	8	15.999	1
atom	191	74	C	"Dimethyl Sulfoxide CH3"	6	12.011	4
atom	192	75	H	"Dimethyl Sulfoxide H3C"	1	1.008	1
vdw	72			3.9100	0.3850		
vdw	73			3.5200	0.1120		
vdw	74			3.8200	0.1010		
vdw	75			2.9100	0.0245	0.910	
bond	72	73		494.20	1.5100		
bond	72	74		197.20	1.8062		
bond	74	75		388.20	1.0893		
angle	73	72	74	57.25	106.88		
angle	74	72	74	87.39	92.98		
angle	72	74	75	44.07	107.06		
angle	75	74	75	38.95	110.07		
strbnd	73	72	74	-5.75	-5.75		
strbnd	74	72	74	-5.75	-5.75		
strbnd	72	74	75	11.50	11.50		
torsion	73	72	74	75	0.000	0.0	1
0.0					0.000	180.0	2
0.0							0.500
torsion	74	72	74	75	0.000	0.0	1
0.0					0.000	180.0	2
0.0							0.500
multipole	189	190	-191	-191	0.28761		
					0.34263	0.00000	0.97464
					-0.69101		
					0.00000	0.85372	
					-0.23783	0.00000	-0.16271
multipole	190	189	-191	-191	-0.63423		
					-0.03435	0.00000	0.26755
					-0.60034		
					0.00000	-0.57370	
					0.09678	0.00000	1.17404
multipole	191	189	190		-0.05355		
					-0.08789	0.00000	0.54241
					-0.28219		
					0.00000	-0.59075	
					-0.20358	0.00000	0.87294
multipole	192	191	189		0.07562		
					-0.01297	0.00000	-0.15656
					0.08665		
					0.00000	0.07386	
					0.01776	0.00000	-0.16051
polarize	189			3.3000	0.3900	190	191
polarize	190			0.8370	0.3900	189	
polarize	191			1.3340	0.3900	189	192
polarize	192			0.4960	0.3900	191	

5.4. Hexanes

atom	29	27	C	"Alkane CH3-"	6	12.011	4				
atom	30	28	H	"Alkane H3C-"	1	1.008	1				
atom	31	29	C	"Alkane -CH2-"	6	12.011	4				
atom	32	30	H	"Alkane -H2C-"	1	1.008	1				
vdw	27			3.8200	0.1010						
vdw	28			2.9600	0.0240	0.920					
vdw	29			3.8200	0.1010						
vdw	30			2.9800	0.0240	0.940					
bond	27	28		341.00	1.1020						
bond	27	29		323.00	1.5247						
bond	29	29		323.00	1.5247						
bond	29	30		341.00	1.1120						
angle	28	27	28	39.57	107.60	107.80	109.47				
angle	28	27	29	42.44	109.80	109.31	110.70				
angle	27	29	29	48.20	109.50	110.20	111.00				
angle	29	29	29	48.20	109.50	110.20	111.00				
angle	27	29	30	42.44	109.80	109.31	110.70				
angle	29	29	30	42.44	109.80	109.31	110.70				
angle	30	29	30	39.57	107.60	107.80	109.47				
strbnd	28	27	29	11.50	11.50						
strbnd	27	29	29	18.70	18.70						
strbnd	29	29	29	18.70	18.70						
strbnd	27	29	30	11.50	11.50						
strbnd	29	29	30	11.50	11.50						
torsion	28	27	29	27	0.000	0.0	1	0.000	180.0	2	0.341
0.0	3										
torsion	28	27	29	29	0.000	0.0	1	0.000	180.0	2	0.341
0.0	3										
torsion	28	27	29	30	0.000	0.0	1	0.000	180.0	2	0.299
0.0	3										
torsion	27	29	29	27	0.854	0.0	1	-0.374	180.0	2	0.108
0.0	3										
torsion	27	29	29	29	0.854	0.0	1	-0.374	180.0	2	0.108
0.0	3										
torsion	27	29	29	30	0.000	0.0	1	0.000	180.0	2	0.341
0.0	3										
torsion	29	29	29	29	0.854	0.0	1	-0.374	180.0	2	0.108
0.0	3										
torsion	29	29	29	79	0.854	0.0	1	-0.374	180.0	2	0.108
0.0	3										
torsion	29	29	29	30	0.000	0.0	1	0.000	180.0	2	0.108
0.0	3										
torsion	30	29	29	30	0.000	0.0	1	0.000	180.0	2	0.299
0.0	3										
multipole	29	31	30		-0.16638						
					0.00000	0.00000		0.25069			
					-0.24574						
					0.00000	-0.24574					
					0.00000	0.00000		0.49148			
multipole	30	29	31		0.05546						

				0.01102	0.00000	-0.10399
				0.00247		
				0.00000	-0.01906	
				0.00852	0.00000	0.01659
multipole	31	31	29	-0.12028		
				0.33700	0.00000	0.22666
				0.34191		
				0.00000	-0.72407	
				-0.04985	0.00000	0.38216
multipole	31	-31	-31	-0.12028		
				0.00000	0.00000	0.27522
				0.47728		
				0.00000	-0.35302	
				0.00000	0.00000	-0.12426
multipole	32	31	31	0.06014		
				0.00606	0.00000	-0.08554
				-0.00370		
				0.00000	-0.01833	
				0.00546	0.00000	0.02203
polarize	29		1.3340	0.3900	30	
polarize	30		0.4960	0.3900	29	
polarize	31		1.3340	0.3900	32	
polarize	32		0.4960	0.3900	31	

torsion	29	29	29	29	0.854	0.0	1	-0.374	180.0	2	0.108
0.0 3											
torsion	29	29	29	79	0.854	0.0	1	-0.374	180.0	2	0.108
0.0 3											
torsion	29	29	29	30	0.000	0.0	1	0.000	180.0	2	0.108
0.0 3											
torsion	79	29	29	30	0.000	0.0	1	0.000	180.0	2	0.108
0.0 3											
torsion	30	29	29	30	0.000	0.0	1	0.000	180.0	2	0.299
0.0 3											
torsion	80	79	29	30	0.000	0.0	1	0.000	180.0	2	0.000
0.0 3											
torsion	80	79	29	29	0.000	0.0	1	0.000	180.0	2	0.000
0.0 3											
multipole	29	31	30		-0.16638						
					0.00000			0.00000			0.25069
					-0.24574						
					0.00000			-0.24574			
multipole	30	29	31		0.00000			0.00000			0.49148
					0.05546						
					0.01102			0.00000			-0.10399
					0.00247						
					0.00000			-0.01906			
multipole	31	31	29		0.00852			0.00000			0.01659
					-0.12028						
					0.33700			0.00000			0.22666
					0.34191						
					0.00000			-0.72407			
multipole	31	-31	-31		-0.04985			0.00000			0.38216
					-0.12028						
					0.00000			0.00000			0.27522
					0.47728						
					0.00000			-0.35302			
multipole	32	31	31		0.00000			0.00000			-0.12426
					0.06014						
					0.00606			0.00000			-0.08554
					-0.00370						
					0.00000			-0.01833			
multipole	210	211	0		0.00546			0.00000			0.02203
					0.50893						
					0.00000			0.00000			0.00838
					0.04512						
					0.00000			0.04512			
multipole	211	210	0		0.00000			0.00000			-0.09024
					-0.64934						
					0.00000			0.00000			-0.41663
					0.40285						
					0.00000			0.40285			
multipole	33	210	0		0.00000			0.00000			-0.80570
					-0.16117						
					0.00000			0.00000			0.17034
					-0.03526						
					0.00000			-0.03526			
multipole	34	33	210		0.00000			0.00000			0.07052
					0.15079						
					0.00543			0.00000			-0.12249

0.11906		
0.00000	0.00913	
0.02813	0.00000	-0.12819

polarize	29	1.3340	0.3900	30
polarize	30	0.4960	0.3900	29
polarize	31	1.3340	0.3900	32
polarize	32	0.4960	0.3900	31
polarize	33	1.3340	0.3900	210 34
polarize	34	0.4960	0.3900	33
polarize	210	1.3340	0.3900	211 33
polarize	211	1.0730	0.3900	210

torsion	5	3	3	5	0.000	0.0	1	0.000	180.0	2	0.150
0.0 3											
multipole	1	2	3		0.09445			0.00000		0.35135	
					0.02472						
					-0.15743						
					0.00000			-0.34410			
multipole	2	-1	-1		-0.27885			0.00000		0.50153	
					-0.29982						
					-0.00033			0.00000		0.59272	
					0.35733						
					0.00000			-0.67646			
multipole	3	1	3		0.00000			0.00000		0.31913	
					-0.19057						
					0.24073			0.00000		0.23156	
					0.21094						
					0.00000			-0.33542			
multipole	4	1	2		-0.25214			0.00000		0.12448	
					0.03649						
					-0.01885			0.00000		-0.10133	
					0.05488						
					0.00000			0.13188			
multipole	5	3	1		-0.08609			0.00000		-0.18676	
					0.08357						
					0.00299			0.00000		-0.07326	
					0.14804						
					0.00000			0.01303			
					-0.05098			0.00000		-0.16107	
polarize	1		1.3340		0.3900		2		4		
polarize	2		0.8370		0.3900		1				
polarize	3		1.3340		0.3900		5				
polarize	4		0.4960		0.3900		1				
polarize	5		0.4960		0.3900		3				

5.7. Acetophenone

atom	101	101	C	"ACPH C4	"	6	12.011	3
atom	102	102	C	"ACPH C3	"	6	12.011	3
atom	103	103	C	"ACPH C2	"	6	12.011	3
atom	104	104	C	"ACPH C1	"	6	12.011	3
atom	107	107	H	"ACPH H3	"	1	1.008	1
atom	108	108	H	"ACPH H2	"	1	1.008	1
atom	111	111	C	"ACPH C(CO)	"	6	12.011	3
atom	112	112	C	"ACPH C(CH3)	"	6	12.011	4
atom	115	115	H	"ACPH H(CH3)	"	1	1.008	1
atom	116	116	O	"ACPH O(CO)	"	8	15.999	1
atom	117	117	H	"ACPH H4	"	1	1.008	1
vdw	101			3.800	0.0910			
vdw	102			3.800	0.0910			
vdw	103			3.800	0.0910			
vdw	104			3.800	0.0910			
vdw	107			2.980	0.0260	0.92		
vdw	108			2.980	0.0260	0.92		
vdw	111			3.800	0.0910			
vdw	112			3.820	0.1010			
vdw	115			2.960	0.0240	0.92		
vdw	116			3.300	0.1120			
vdw	117			2.960	0.0260	0.92		
bond	101	102		680.0	1.3947			
bond	101	117		410.0	1.0822			
bond	102	103		680.0	1.3915			
bond	102	107		410.0	1.0822			
bond	103	104		680.0	1.3992			
bond	103	108		410.0	1.0819			
bond	104	111		680.0	1.4940			
bond	111	112		385.0	1.5085			
bond	111	116		680.0	1.2237			
bond	112	115		400.0	1.0888			
angle	102	101	102	60.00	119.90			
angle	102	101	117	32.00	120.05			
angle	101	102	103	60.00	120.11			
angle	101	102	107	32.00	119.98			
angle	103	102	107	32.00	119.91			
angle	102	103	104	60.00	120.19			
angle	102	103	108	32.00	120.43			
angle	104	103	108	32.00	119.37			
angle	103	104	103	60.00	119.50			
angle	103	104	111	60.00	120.25			
angle	104	111	112	60.00	118.35			
angle	104	111	116	60.00	120.69			
angle	112	111	116	60.00	120.97			
angle	111	112	115	38.00	109.91			
angle	115	112	115	34.50	109.03			
strbnd	102	101	102	18.70	18.70			
strbnd	102	101	117	18.70	11.50			
strbnd	101	102	103	18.70	18.70			
strbnd	101	102	107	18.70	11.50			
strbnd	103	102	107	18.70	11.50			

multipole	101	-102	-102	-0.02570		
				0.00768	0.00000	-0.01753
				0.21266		
				0.00000	-0.16041	
				0.00442	0.00000	-0.05225
multipole	102	-101	-103	0.03891		
				0.02722	0.00000	0.14297
				-0.04801		
				0.00000	-0.26527	
				-0.06576	0.00000	0.31328
multipole	103	-102	-104	-0.00467		
				0.10264	0.00000	0.06877
				0.09548		
				0.00000	-0.16435	
				-0.13677	0.00000	0.06886
multipole	104	111	103	-0.19836		
				0.10216	0.00000	0.09151
				-0.04074		
				0.00000	0.02610	
				0.01242	0.00000	0.01464
multipole	107	102	101	0.01016		
				-0.00065	0.00000	-0.17629
				0.12054		
				0.00000	0.06309	
				-0.00762	0.00000	-0.18362
multipole	108	103	102	0.039795		
				-0.00208	0.00000	-0.13374
				0.10762		
				0.00000	0.02400	
				-0.10670	0.00000	-0.13162
multipole	111	116	104	0.76904		
				0.21969	0.00000	0.59927
				0.31546		
				0.00000	-0.31422	
				0.49622	0.00000	-0.00124
multipole	112	111	113	-0.27307		
				-0.02897	0.00000	0.21491
				-0.11113		
				0.00000	0.04609	
				0.02550	0.00000	0.06504
multipole	115	112	111	0.08196		
				-0.00144	0.00000	-0.08391
				0.06581		
				0.00000	0.00381	
				-0.04427	0.00000	-0.06962
multipole	116	111	104	-0.69483		
				-0.15120	0.00000	-0.22092
				-0.71841		
				0.00000	0.46814	
				-0.20408	0.00000	0.25027
multipole	117	101	102	0.00865		
				0.00321	0.00000	-0.18157
				0.10658		
				0.00000	0.02986	
				0.00449	0.00000	-0.13644
polarize	101		1.7500	0.3900	102	117

polarize	102	1.7500	0.3900	101	103	107
polarize	103	1.7500	0.3900	102	104	108
polarize	104	1.7500	0.3900	103		
polarize	107	0.6960	0.3900	102		
polarize	108	0.6960	0.3900	103		
polarize	111	1.3340	0.3900	116		
polarize	112	1.3340	0.3900	113		
polarize	115	0.4960	0.3900	112		
polarize	116	0.8370	0.3900	111		
polarize	117	0.6960	0.3900	101		