A Many-Body Perspective of Nuclear Quantum Effects in Aqueous Clusters

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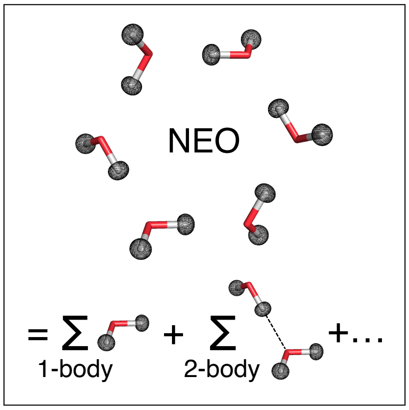
Abstract

Nuclear quantum effects play an important role in the structure and thermodynamics of aqueous systems. By performing a many-body expansion with nuclear-electronic orbital (NEO) theory, we show that proton quantization can give rise to significant energetic contributions for many-body interactions spanning several molecules in single-point energy calculations of water clusters. Although zero-point motion produces a large increase in energy at the one-body level, nuclear quantum effects serve to stabilize molecular interactions at higher orders. These results are significant because they demonstrate that nuclear quantum effects play a nontrivial role in many-body interactions of aqueous systems. Our approach also provides a pathway to incorporate nuclear quantum effects into water potential energy surfaces. The NEO approach is advantageous for many-body expansion analyses because it includes nuclear quantum effects directly into the energies.

Graphical TOC Entry



Nuclear quantum effects play a crucial role in intermolecular interactions for many chemical and biological systems, particularly those with hydrogen bonding.[1–9] Including such effects is therefore necessary for a fundamentally correct description of the interactions in a molecular simulation. Moreover, nuclear quantum effects have been shown to be necessary to capture important structural and dynamical effects in the thermodynamic regime.[10–13] For example, nuclear quantization weakens hydrogen bonds in liquid water,[14] resulting in a less dense condensed phase,[12] as well as a red shift of peak positions in the infrared and sum frequency generation spectra.[15,16]

Incorporating nuclear quantum effects into chemical calculations is a longstanding challenge in the field. Path integral methods have been used to tackle this problem in equilibrium molecular dynamics simulations[17] and to study the energy landscape of water clusters.[18] However, this formalism does not provide an explicit nuclear wavefunction[19] and poses certain challenges in describing excited electronic states and non-Born-Oppenheimer processes.[20] Other approaches, including exact factorization[21] and the multiconfigurational time-dependent Hartree method,[22] have also been used to describe nuclear quantum effects but have not seen widespread adoption due to their cost and complexity.

The nuclear–electronic orbital (NEO) method can be used to directly incorporate certain nuclear quantum effects into calculations of chemical and biological systems based on density functional theory (DFT) or wavefunction theories. The NEO approach is attractive because the electronic and quantum nuclear components are treated on the same quantum mechanical footing, thereby avoiding the Born-Oppenheimer separation between electrons and quantum nuclei. Typically, the quantum nuclei are protons, and the NEO approach inherently accounts for delocalization and the zero-point energy associated with these nuclei. The NEO approach is particularly useful for processes in the nonadiabatic regime, such as proton-coupled electron transfer or hydrogen tunneling. The NEO approach has been derived for Hartree-Fock and density functional theories,[23–26] as well as for more advanced wavefunction approaches, including second-order Møller-Plesset perturbation theory (MP2) and coupled cluster theory with single and double excitations (CCSD).[27–30] For the investigation of dynamical processes, the NEO approach has been adapted for the real-time (RT) propagation of the electronic and quantum nuclear subsystems in the RT-NEO method,[31] often in conjunction with NEO-Ehrenfest dynamics.[32–34]

In this work, the interaction energies of water clusters are examined through the lens of a many-body decomposition, with nuclear quantum effects included explicitly through the NEO formalism. The many-body expansion (MBE) rigorously decomposes the interaction energy into the individual contributions stemming from monomers, pairwise interactions, and all other higher-order interactions among molecules.[35] This expansion accounts for the gradual emergence of condensed phase behavior through the systematic inclusion of higher-order interactions in molecular clusters. The NEO approach has been used previously to demonstrate that the single-point energetic ordering of protonated water cluster isomers qualitatively changes with proton quantization.[36,37] Because the NEO method rigorously includes nuclear quantization in single-point energy calculations, it naturally allows for energetic decomposition and corresponding analysis.

Although significant effort has been directed toward examining the impact of nuclear effects on the structural and thermodynamic properties of water across different phases using molecular mechanical potentials,[5,38–41] the energetic impact of nuclear quantum effects within the MBE has not yet been systematically characterized. By analyzing the many-body contributions to the energy, we uncover the long-range contributions stemming from proton quantization in water clusters. These analyses have the potential to provide a deeper understanding of the complex and long-range effects of nuclear quantization. Finally, the formalism introduced in this study provides a computationally efficient, alternative path to including nuclear quantum effects in molecular mechanical schemes by directly including the corresponding energetic contributions within the molecular mechanical representation.

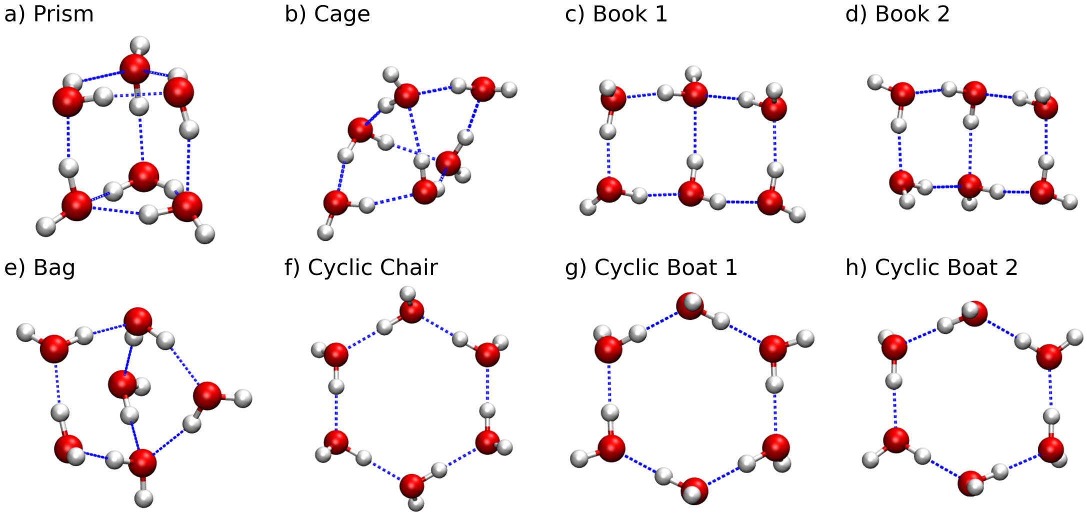


Figure 1. Structures of the eight water hexamers used in this MBE analysis.

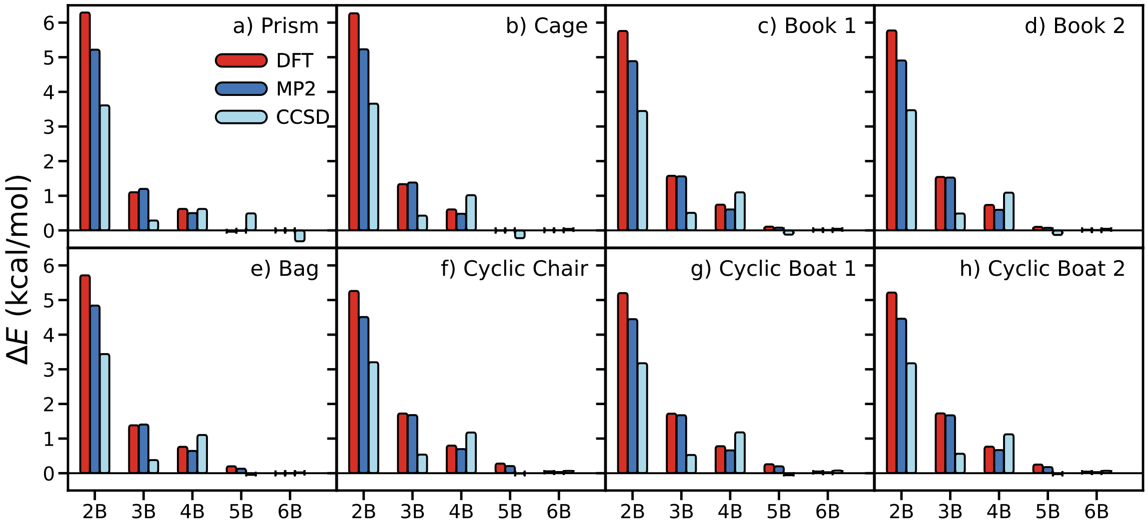


Figure 2. Difference between the conventional DFT, MP2, and CCSD n-body energies $\epsilon_{n\mathrm{B}}$ (see Eq. (2)) and the corresponding NEO-DFT, NEO-MP2, and NEO-CCSD n-body energies. The six lowest energy MP2 optimized water hexamers used in this analysis (see Figure 1) are labeled in each panel.

The MBE is written as

$$E_N(\mathbf{r}_1,..,\mathbf{r}_N) = \sum_{i=1}^{N} \epsilon_{1\mathrm{B}}(\mathbf{r}_i) + \sum_{i<j}^{N} \epsilon_{2\mathrm{B}}(\mathbf{r}_i,\mathbf{r}_j) + \sum_{i<j<k}^{N} \epsilon_{3\mathrm{B}}(\mathbf{r}_i,\mathbf{r}_j,\mathbf{r}_k) + ... + \epsilon_{N\mathrm{B}}(\mathbf{r}_1,..,\mathbf{r}_N) \quad (1)$$

where $\mathbf{r}_i$ represents the coordinates of the monomer i within the cluster, and $\epsilon_{1\mathrm{B}}(\mathbf{r}_i)$ represents the energy of the monomer at the geometry $\mathbf{r}_i$. The n-body energies $\epsilon_{n\mathrm{B}}$ with $n > 1$ are recursively defined as:

$$\epsilon_{n\mathrm{B}}(\mathbf{r}_i,\mathbf{r}_j,...) = E_n(\mathbf{r}_i,\mathbf{r}_j,...) - \sum_{i=1}^{n} \epsilon_{1\mathrm{B}}(\mathbf{r}_i) - \sum_{i<j}^{n} \epsilon_{2\mathrm{B}}(\mathbf{r}_i,\mathbf{r}_j) - ... - \sum_{i<j<k<...}^{n} \epsilon_{(n-1)\mathrm{B}}(\mathbf{r}_i,\mathbf{r}_j,...). \quad (2)$$

Here $E_n(\mathbf{r}_i,\mathbf{r}_j,...)$ is the energy of the n-body cluster with specified coordinates for the n monomers, and $\epsilon_{n\mathrm{B}}(\mathbf{r}_i,\mathbf{r}_j,...)$ is the difference between this n-body cluster energy and the sum of the associated fragments up to $(n-1)$-body terms. The MBE converges rapidly for typical molecular clusters composed of molecules with large band gaps, such as water and other non-conductive species. In principle, this allows the potential energy surface associated with the system to be efficiently represented as an explicit sum of the low-order terms of the expansion with the higher-order terms being implicitly captured by simple classical polarization. The MBE has been a critical tool in developing a generation of many-body polarizable models,[42] particularly for aqueous systems, such as the AMOEBA,[43,44] iAMOEBA,[45] TTMn-F,[46–50] HBB-pol,[51,52] WHBB,[53,54] CC-pol,[55] MB-nrg,[56–60] and MB-pol[61] models, among others.

In our MBE analysis within the NEO framework, we consider the low-energy isomers of the water hexamer, $(H_2O)_6$, to provide fundamental insight into the many-body physics in aqueous systems. The eight lowest-energy structures optimized at the conventional MP2 level of theory are used.[12,62,63] A schematic of these structures is given in Figure 1. We performed calculations of the MBE components using NEO-DFT, NEO-MP2, and NEO-CCSD, as well as the respective conventional (single-component electronic) equivalent methods. The NEO-DFT calculations were conducted using a development version of ChronusQ,[64] whereas the NEO-MP2 and NEO-CCSD calculations were conducted using a development version of

Q-Chem.[65] The implementations of NEO-DFT in ChronusQ and Q-Chem have been cross-validated against each other. The cc-pVTZ electronic basis set[66] and the PB4-D protonic basis set[67] were used for all NEO calculations. The PBE0 electronic exchange-correlation functional[68] and the epc17-2 electron-proton correlation functional[26] were used in the NEO-DFT calculations with a (99,590) integration grid. The NEO-CCSD and NEO-MP2 calculations were performed with density fitting using the RI-cc-pVTZ electronic auxiliary basis.[69] For the protonic auxiliary basis, a 12s8p8d even-tempered basis was used with exponents from $\sqrt{2}$ to 64 for the s functions and $2\sqrt{2}$ to 32 for the p and d functions. For the NEO calculations, the basis functions associated with the quantum protons were centered at the positions of the classical nuclei in the geometries optimized at the MP2 level. Geometry optimizations of the individual fragments were not performed in an effort to maintain consistency throughout the many-body analysis. Conventional DFT, MP2, and CCSD calculations were performed using the same software packages, electronic basis sets, and functionals as previously described for their NEO counterparts.

To analyze the energetic effects of proton quantization in these water hexamers, we examine the differences in the n-body energies between NEO and conventional electronic structure calculations. The difference is computed as

$$\Delta E = E_{n\mathrm{B}}^{\mathrm{Conv.}} - E_{n\mathrm{B}}^{\mathrm{NEO}} \tag{3}$$

where $E_{n\mathrm{B}}$ is defined as the sum over $\epsilon_{n\mathrm{B}}$ for all n-mers within the cluster (*i.e.*, the first, second, and third terms on the right side of Eq. (1) for $n = 1$, 2, and 3, respectively). Thus, ΔE describes how the conventional n-body interaction energy deviates from the corresponding NEO reference value, quantifying the impact of nuclear quantum effects in each many-body term.

The results of ΔE computed with NEO-DFT, NEO-MP2, NEO-CCSD, and their respective conventional electronic structure counterparts are shown in Figure 2. The 1B contributions, which are not shown in Figure 2, produce a negative ΔE on the order of 100 kcal/mol for all levels of theory, corresponding to a higher NEO energy due to the total zero-point energy of the O-H vibrations in the individual water molecules. The 2B interaction energies produce a significant positive ΔE for all isomers and at all levels of theory. The impact of nuclear quantum effects on the 2B interactions corresponds to the influence of proton quantization on pairwise hydrogen bonding between adjacent water molecules. The 2B ΔE lies between $\sim$3 and 6 kcal/mol over the eight hexamers and three levels of theory, with NEO-DFT producing the largest differences, followed by NEO-MP2, and finally NEO-CCSD with the smallest differences. The positive sign indicates a net stabilizing effect due to nuclear quantum effects at the 2B level.

Although ΔE becomes smaller for higher-order n-body interactions, the 3B and 4B terms still exhibit nuclear quantum effects of $\sim$ 1 kcal/mol. We note that while the absolute value of ΔE is smaller for the 3B and 4B terms, it actually accounts for a larger percentage of the energy for each term. We include an analysis of ΔE as a percentage of each $E_{n\mathrm{B}}$ in Table S1 of the SI. Similarly to the 2B interaction energy, the 3B and 4B terms also exhibit a stabilizing effect due to nuclear quantization across all isomers and all levels of theory. This stabilizing effect arises mainly from the influence of one hydrogen-bonding interaction on another hydrogen-bonding interaction within the water cluster. It has been shown that 4B terms still play important roles in the energetics of water clusters at the CCSD(T) level, with explicit 4B representations incorporated in recent water models.[70,71] Thus, the observation of nuclear quantum effects at the 4B level may be significant in the context of these water models.

In these results, similar trends are broadly observed at the DFT, MP2, and CCSD levels of theory. This finding suggests that the nuclear quantum effects observed in this study are not artifacts of one specific method. For the 2B and 3B terms, DFT shows the largest effects, whereas CCSD shows the smallest effects. For the 4B terms, CCSD displays the largest effects, breaking the trend of monotonically decreasing nuclear quantum contributions for higher-order terms. The energy difference ΔE for the CCSD 4B terms is particularly large, exceeding 1 kcal/mol for all but the prism isomer. The cause of the non-monotonic trend in the NEO-CCSD ΔE is unclear. Analysis of the individual 3B interactions at the NEO-CCSD level shows that although the sum of the 3B terms has a net positive ΔE, indicating stabilization by nuclear quantum effects, only trimer fragments that are continuously hydrogen bonded contribute positive values, with all other trimers giving slightly negative contributions. In contrast, NEO-MP2 and NEO-DFT produce a positive ΔE for all trimer fragments, regardless of the bonding arrangement. For the individual 4B terms, NEO-CCSD contributes a large positive ΔE, exceeding the contributions of NEO-MP2 and NEO-DFT, for all individual 4B terms. Note that all clusters are at a fixed geometry optimized at the conventional MP2 level. Optimizing the geometries at a different level of theory, such as conventional CCSD, or with a NEO method, could change the detailed results, although the qualitative observations are expected to be robust. An MBE analysis for geometries optimized at the NEO-DFT level of theory is provided in Figure S2 of the SI.

Although nuclear quantum effects are still found at the 5B and 6B level, the interaction energies are generally well below 0.5 kcal/mol, so we can consider the MBE largely converged by this point. The notable exception is the prism isomer, which displays anomalously high 5B and 6B nuclear quantum effects at the NEO-CCSD level, and is the only isomer with a positive 5B ΔE at this level. This behavior likely arises because the prism isomer has nine hydrogen bonds, more than any of the other hexamers studied. A more detailed analysis of these higher-order contributions at the NEO-CCSD level provides further insights. The cage isomer, which has eight hydrogen bonds, has the second largest 5B and 6B contributions, followed by the book and bag isomers, which have seven hydrogen bonds. Finally, the set of cyclic isomers, which have only six hydrogen bonds, have negligible 5B and 6B contributions. While NEO-CCSD follows the physically intuitive trend of 5- and 6-body energies directly correlating to number of hydrogen bonds, the more approximate NEO-DFT and NEO-MP2 do not, indicating that NEO-CCSD may more precisely capture long-range effects. Further-more, although nuclear quantum effects have been shown to alter the energetic ordering of protonated water clusters,[36,37] nuclear quantum effects do not affect the relative energetic ordering of the eight neutral water isomers studied herein with respect to total energy or interaction energy, as shown in Figure S3 of the SI.

In calculations of molecular interaction energies, electronic basis set superposition error (BSSE) can affect the energetics. BSSE in water clusters can be mitigated by using a more complete basis set or treated with methods such as the counterpoise correction.[72,73] In NEO calculations, protonic BSSE should not be important due to the high spatial localization of the proton density. Although all calculations presented in this manuscript were performed with the cc-pVTZ and PB4-D basis sets, we performed test calculations on smaller clusters with the aug-cc-pVTZ and PB5-D basis sets and found that increasing the basis set size produced almost no change in ΔE. Indeed, the apparent BSSE should be minimal because we are analyzing the energy *differences* between NEO and conventional electronic structure calculations. Both approaches used the same method and basis set to describe the electronic wavefunction, and therefore any purely electronic BSSE contributions should mostly cancel out in our results. To test our assumption, we performed MBE calculations up to the 4B terms with larger basis sets, namely the cc-pVQZ electronic basis set and the PB5-D protonic basis set. These results are provided in Figure S1 of the SI. We find that using a larger basis set leads to the same qualitative conclusions. Note that electronic BSSE corrections would need to be considered for calculations that use the raw NEO energies, for example to compute a many-body potential energy surface.

This Letter highlights the importance of proton quantization for an accurate description of the intermolecular interactions occurring within water clusters. Our calculations show that conventional electronic structure methods lack some long-range many-body contributions inherent to calculations with quantized protons, such as the NEO-DFT, NEO-MP2, and NEO-CCSD methods. The energetic contributions from proton quantization are significant in magnitude even for relatively high order many-body terms, exceeding 1 kcal/mol for the four-body terms. Because quantized protons are typically localized relative to the electrons, these effects may arise from longer-range electronic interactions enabled by proton quantization. This type of analysis can provide fundamental insight into the interplay between nuclear quantum effects and system size, allowing for a systematic analysis of nuclear quantum effects in clusters of increasing size toward the condensed phase.

The results presented in this work illustrate the importance of nuclear quantum effects for long-range many-body interactions within water clusters and demonstrate that the NEO method can be used to analyze such nuclear quantum effects within a many-body perspective. This study also provides a path forward on how to incorporate nuclear quantum effects naturally in data driven many-body molecular mechanics approaches such as in the MB-*nrg* or MB-DFT models. By training the many-body terms of these models on data sets calculated with NEO-DFT, NEO-MP2, or NEO-CCSD, nuclear quantum effects can be naturally incorporated in this class of models. In such cases, the nuclear dynamics should be treated classically to avoid double counting of the nuclear quantum effects. Although such an approach is approximate, it is significantly more computationally efficient than quantum dynamical simulations and could be useful for studying large condensed phase systems.

Supporting Information Available

The Supporting Information is available free of charge:

Structures of the water hexamers studied (.zip)

The effect of a larger protonic and electronic basis set; the effect of optimizing hexamer geometry with NEO-DFT; percent difference between $E_{n\mathrm{B}}^{\mathrm{NEO}}$ and $E_{n\mathrm{B}}^{\mathrm{conv}}$; relative energies of the eight water clusters studied (PDF)

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