Toward a Consistent Treatment of Polarization in Model QM/MM Calculations

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The concept of model chemistries within hybrid QM/MM calculations has been addressed through analysis of the polarization energy determined by two distinct approaches based on (i) induced charges and (ii) induced dipoles. The quantum mechanical polarization energy for four configurations of the water dimer has been determined for a range of basis sets using Morokuma energy decomposition analysis. This benchmark value has been compared to the fully classical polarization energy determined using the induced dipole approach, and the molecular mechanics polarization energy calculated using induced charges within the MM region of hybrid QM/MM calculations. From the water dimer calculations, it is concluded that the induced charge approach is consistent with medium sized basis set calculations whereas the induced dipole approach is consistent with large basis set calculations. This result is highly relevant to the concept of QM/MM model chemistries.

Introduction

The use of quantum mechanics in quantum mechanical model chemistries has greatly simplified the systematic study of trends within a series of similar compounds and has led to a clear understanding of the strengths and weaknesses of such models. Thus the use of the historically important but relatively inaccurate STO-3G basis set[1] is no longer widespread. In contrast, the G1,[2] G2[3] and G3[4] methods that employ large basis sets and extensive treatment of electron correlation are highly accurate but also have relatively restricted use because of the computational expense of the methods. For practical applications on large molecules, a compromise is required, typically using a basis set of double-ζ quality with added polarization functions. Consequently, the 6-31G* family of basis sets[5] lies at the heart of many calculations on biomolecular systems.

Within classical approaches, such a systematic hierarchy of models is not well-defined, though parameters such as the length of a simulation are pertinent. The lack of a systematic hierarchy is generally not a problem, as the movement toward accuracy is usually achieved through improvements in parametrization rather than through increasing levels of theory.[6] However, there is potentially a problem when classical and quantum methods are combined within QM/MM approaches because there is a requirement that the parametrization should be consistent with the level of theory used. Developments of classical force fields to include polarization have been understood for over 30 years; e.g., see ref 7. These are usually based on induced dipoles, though approaches to polarization based on fluctuating charges, the related chemical potential equalization model and the Drude oscillator model have also been used,[8−14] and some of these have been included in hybrid QM/MM methods.[15] Here we focus on three approaches to polarization, namely neglect, the induced charge approach,[16−18] and the induced dipole approach,[19] and investigate the extent to which these are compatible with a range of quantum mechanical model chemistries ranging from small basis set to large basis set Hartree−Fock calculations. A number of the larger basis sets were designed for use with correlated wave functions[20] or with density functional methods,[21] but here our quantification of the quantum mechanical polarization energy will be carried out using Morokuma energy decomposition analysis[22] and hence our calculations will be at the restricted Hartree−Fock level.[23] The primary system chosen for study is water, because well parametrized three point induced charge[16] and induced dipole[24] water models exist, even though water presents particularly difficult theoretical challenges because the geometries offer the potential to expose the limitations in the induced charge model.

Methods

Atomic polarization is usually modeled using eq 1, where the vector μ is the induced dipole, α is the isotropic polarizability, here taken from Miller and Savchik,[25] and E is the electric field vector at the atom due to the surrounding atoms (which are usually not bonded directly).

$$\mu = \alpha E \qquad (1)$$

Because the induced dipoles at other centers contribute to the field, E, eq 1 is usually iterated to convergence, though iteration can often be omitted with little loss of accuracy.[26,27]

For the purposes of this paper, three separate models for polarization were used for comparison against one another, within the framework of a QM/MM calculation. First, following the approach above, the field E, from eq 1, was calculated from the electronic distribution of the QM region, and this was used to determine induced dipoles, μ, at each of the points in the MM region. The polarization energy in this case, denoted

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$E_{\mathrm{pol}}(\mu)$, was defined as the self-energy of the dipoles, calculated purely classically over both water molecules (i.e., without either MM part polarizing the other QM part). Second, the induced charge method of polarization[16] was used to represent the polarization using point charges. As in the first method, dipoles were calculated at each of the atomic centers in the MM region. Previously developed methods for calculating potential-derived point charges from a distributed multipole analysis[18] were then applied to express each of the induced dipoles as a set of "induced" charges on the atom carrying the polarizability, α, and those bonded to it (which in some calculations included off-atom centers). These induced charges were then fed back into the QM/MM system, and the QM part of the system was reconverged with these new MM charges. The polarization energy in this second method, denoted $E_{\mathrm{pol}}(q)$, was defined as the sum of two parts, representing the polarization of the QM and the MM parts of the system, respectively. The QM part of the polarization energy was defined as the change in the energy of the QM part of the system resulting from the introduction of the induced MM charges, calculated before and after by subtracting the self-energy of the MM charges from the energy of the QM/MM system. The system was then iterated, allowing for feedback between the QM and MM regions until convergence, and the converged energy of the QM/MM system was again calculated, the MM part of the polarization being defined as half the difference in energy resulting from the iteration of the charges. In a third, and final method, the effects of polarization were neglected entirely, resulting trivially in a polarization energy of zero.

To determine a benchmark polarization energy, Morokuma energy decomposition analysis as implemented in GAMESS (US) was carried out at the optimized geometry to determine the quantum mechanical polarization energy, $E_{\mathrm{pol}}(\mathrm{QM})$. This was compared to the polarization energies calculated for the induced dipoles, and for the induced charges, $E_{\mathrm{pol}}(\mu)$ and $E_{\mathrm{pol}}(\mathrm{q})$, respectively.

Within the induced charge model, the second of those described above, the induced charges are determined to reproduce the induced dipole of eq 1. For a water molecule, this is very efficient if the field vector and hence the induced dipole has a major component parallel to the plane of the water molecule, but not if there is a major component perpendicular to the plane of the molecule.[27] Consequently, we have studied four water dimer geometries (see Supporting Information Table S1 for coordinates): (a), the fully optimized geometry, (b), the geometry optimized subject to the constraint that the system is planar ($\mathrm{WW}_{\mathrm{planar}}$), and (c), the water molecules A and B optimized such that the oxygen atom of water A ($\mathrm{O_A}$) and a hydrogen of water A ($\mathrm{H_{A1}}$) form a hydrogen bond with water B such that the bond $\mathrm{O_A{-}H_{A1}}$ is perpendicular to the plane of water B, with $\mathrm{O_B}$ colinear with the bond $\mathrm{O_A{-}H_{A1}}$ ($\mathrm{WW}_{\mathrm{perp}}$). In the fourth geometry, (d), the water dimer was optimized to a geometry intermediate between (b) and (c). The optimization was carried out using a TZVP basis set[28] at the B3LYP level;[29] this approach was chosen to minimize basis set superposition effects[30] and to avoid biasing the results in favor of any one method.

Morokuma energy decomposition analysis[22] as implemented in GAMESS (US)[31] was carried out at the optimized geometry to determined the quantum mechanical polarization energy,[16] $E_{\mathrm{pol}}(\mathrm{QM})$. The polarization for the induced charges, $E_{\mathrm{pol}}(q)$, was determined at the hybrid QM/MM level and was determined as one of the two asymmetric determinations[16] (or the average of the two), because either molecule can be the QM entity. The induced dipole polarization energy, $E_{\mathrm{pol}}(\mu)$, was determined classically. The polarization energy error (relative to the Morokuma polarization energy), ΔE_{i}, at each geometry i (i.e., geometries (a) to (d)) and for each method (essentially methods 1 and 2) is therefore given by

$$\Delta E_{\mathrm{i}} = E_{\mathrm{pol}}(\mathrm{QM}) - E_{\mathrm{pol}}(\mathrm{x}) \tag{2}$$

In $E_{\mathrm{pol}}(\mathrm{x})$, x is either q or μ for induced charges or induced dipoles respectively, and the energy includes the self-energy correction.[16] Where polarization is neglected (method 3), the error is simply $E_{\mathrm{pol}}(\mathrm{QM})$. This error is relative to the polarization energy determined using Morokuma energy decomposition analysis at that basis set and is not a true error as within a given model chemistry (i.e., quantum mechanical method and basis set) it is possible large absolute error but a small ΔE_{i} by eq 2. To alleviate this potential confusion, henceforth we refer to ΔE_{i} as a measure of consistency (MOC) value rather than an error. The Bolzmann population, P_{i}, for the four geometries (a)−(d) can then be used to determined an overall weighted measure of consistency, $\Delta E(\mathrm{tot})$, for polarization calculated by either induced charges or induced dipoles, which is given by

$$\Delta E(\mathrm{tot}) = \sum P_{\mathrm{i}} \times \mathrm{abs}(\Delta E_{\mathrm{i}}) \tag{3}$$

Here the absolute value is taken so as to prevent the potential canceling out of errors of opposite sign.

A diverse range of basis sets were used for the calculations, as follows: STO-3G,[1] 3-21G,[32] 6-31G,[33] 6-31++G,[33] 6-31G*,[33] 6-311G,[34] DGDZVP,[28] 6-31G**,[33] cc-pVDZ,[35] 6-31++G**,[33] 6-311G*,[34] 6-311+G*,[34] aug-cc-pVDZ,[35] DGDZVP2,[28] 6-311G**,[34] DGTZVP,[28] 6-311++G**,[34] 6-311G(2df,2pd),[34] Sadlej pVTZ,[36] 6-311++G(2d,2p),[34] cc-pVTZ,[35] 6-311++G(3df,3pd),[34] aug-cc-pVTZ,[35] and Roos DZ.[37] These Hartree−Fock QM/MM calculations were carried out using GAUSSIAN 03.[38]

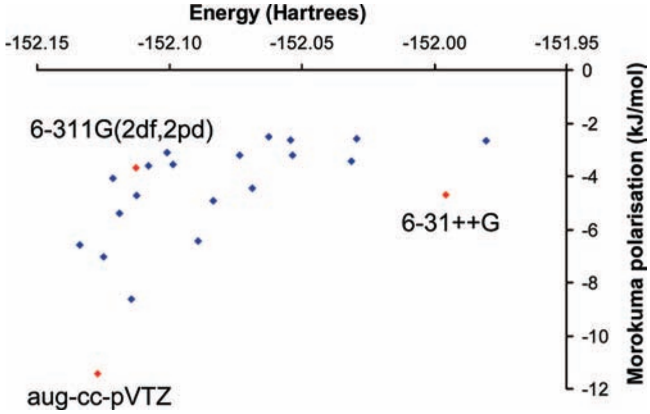

Figure 1. Morokuma polarization energy of an optimized water dimer system plotted against the total energy value for a range of basis sets. Labeled basis sets are marked in red, and other basis sets are marked in blue.

Results

Figure 1 shows the Morokuma polarization energy for the optimized (a, $\mathrm{WW}_{\mathrm{opt}}$) water arrangement for a range of basis sets, compared to the total system energy. It can be seen that the magnitude of the polarization energy generally increases as the basis set is improved, although the increase does not occur in a straightforward way. Diffuse functions (denoted +) rather than polarization functions (denoted *, nd, np) are the most important factor in determining the polarization energy, such that the 6-31++G basis set, which has 10 condensed electron

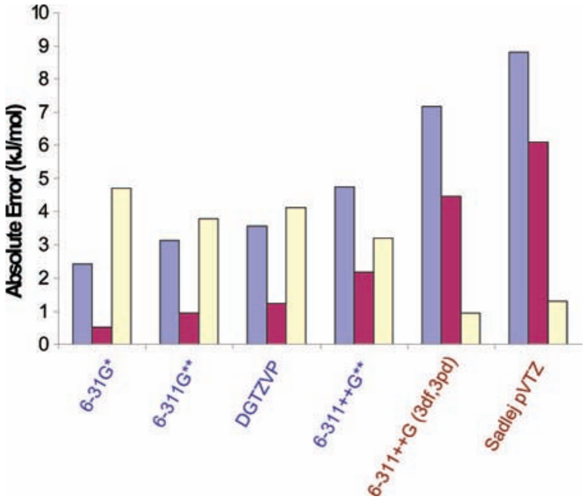

Figure 2. ΔE(tot) (measure of consistency) values for induced charge (left, blue), induced dipole (middle, maroon) and neglect (right, cream) methods. Basis sets for which the induced charge method is the most consistent (smallest ΔE(tot)) are labeled in blue text, and basis sets for which the induced dipole method is the most consistent (smallest ΔE(tot)) are labeled in red text.

shells per water molecule, captures more of the polarization energy than the 6-311G(2df,2pd) basis set, which has 19 condensed electron shells per water, and is the “better” of the two basis sets according to the variational principle. The greatest amount of polarization is captured by highly diffuse basis sets such as aug-cc-pVTZ, which has a polarization energy roughly 3 times greater than 6-311G(2df,2pd). A table of energy values for all of the basis sets tested is given in Supporting Information Table S2, and this shows that the increase in polarization energy with basis set is particularly marked for the perpendicular arrangement (c, WW_{perp}) such that for the small basis sets there is a large difference between the two geometries (e.g., 1.11 kJ mol^{-1} or 72% at the 6-31G level), but that the relative difference decreases markedly for the larger basis sets.

Figure 2 reports the overall weighted error in the polarization energy for the three methods at six different basis sets, ordered by the amount of polarization energy in an optimized water dimer (from Figure 1). For basis sets with a smaller amount of polarization energy, the induced charge method gives the best (lowest) measure of consistency, whereas for basis sets with a larger amount of polarization energy, the dipole method has the best (lowest) measure of consistency. For the first three basis sets recorded, the measure of consistency is surprisingly better (lower) for neglecting polarization completely than for using the induced dipole method.

Measure of consistency values for a wider range of basis sets are displayed in Supporting Information Table S3. At the level of the smallest basis set, e.g., STO-3G, the quantum mechanical polarization energy is so small (0.68 kJ mol^{-1} for the optimized geometry) that it is almost more consistent to neglect polarization than to include the induced charge correction. (Here we note that the STO-3G calculations were carried out at the B3LYP/TZVP geometry and so basis set superposition effects were minimized;[16] at the STO-3G geometry, basis set superposition effects could present as larger polarization effects.) At the 3-21G level or above, it is certainly more consistent to include the induced charge correction than to neglect it, though it would be surprisingly more consistent to ignore the induced dipole correction in a hybrid QM/MM calculation for many basis sets, up to DGTZVP. For intermediate basis sets, e.g., 6-311G**, the induced charge model is the most consistent of the three models. Only with large basis sets such as 6-311++G(3df,3pd) and the Sadlej pVTZ basis set, specifically designed for polarizability calculations, is the treatment of polarization at the induced dipole level more consistent than the induced charge level for a given model chemistry.

These results are molecule specific, as the performance of the induced charge model, but less so the induced dipole model, will depend on both topology and conformation and whether or not critical atoms have sufficient neighboring atoms to reproduce well all components of an induced dipole. Here the water dimer is a severe test and for other molecules, particularly nonplanar ones, the switch from induced charge being more consistent to induced dipole being more consistent may occur at a larger basis set. This effect can be seen in Table 1 where the induced charges often give the lowest (best) measure of consistency for the planar geometry, e.g., with the 6-311++G** and 6-311G(2df,2pd) basis sets whereas the induced dipoles are more likely to give the lowest (best) measure of consistency for the perpendicular geometry, at least with the larger basis sets. One may assume that the perpendicular water system is something of a worst-case scenario as far as induced charges are concerned, but Table 1 indicates that this is not necessarily the case, as shown by the results for moderate sized basis set. Here we note that the induced charge model can be supplemented with off-atomic center charges to increase the accuracy of polarization energy calculations for difficult geometries such as the perpendicular arrangement (geometry c).[27] The effect of these off-atom centers is shown in the Supporting Information where the equivalent of Figure 2 shows that off-atom centers reduces the error for all basis sets apart from 6-31G* (because off-atom centers allow of a more complete description of the electrostatics) and indeed the use of off-atom centers does give the most consistent results (lowest absolute error) for the 6-311G**, DGTZVP and 6-311++G** basis sets. However, the results presented suggest that the use of off-atom centers should only be done given knowledge of the appropriate model chemistry level. We also note from the populations presented in Supporting Information Table S3 that the worst-case scenario perpendicular geometry has a low population of about ∼5 ± 3%, so it is unlikely to make a significant contribution to the mean energy of an ensemble of water molecules. A more comprehensive version of Table 1 is contained in Supporting Information Table S4.

Discussion

The concept of a model chemistry is well understood within applications of quantum chemistry to problems in chemistry and biology, but the realm of classical mechanics is more closely linked to experiment through parametrization. Nevertheless, within the classical realm, the link to model chemistry is frequently retained in the determination of the atomic charges,[39−41] but the danger remains that mixing of terms may arise through parametrization, either by design (as in the use of charges that are too polar to model implicit polarization[42,43] or by accident, e.g., by use of an inappropriate dielectric constant. This process makes it difficult to retain the concept of a model chemistry within the classical domain. Nevertheless, when the two disparate domains are combined, either for the purposes of parametrization or for studying large systems within a hybrid approach, it is important that the combination is appropriate.

Here we have shown that classical polarization, the term that is generally missing from many simulations and hybrid QM/MM calculations on large complex systems, can be combined

TABLE 1: Induced Dipole and QMMM (Induced Charge) Measure of Consistency (MOC) Values for Water Systems in the $\mathrm{WW}_{\mathrm{planar}}$ and $\mathrm{WW}_{\mathrm{perp}}$ Orientations, Modeled Using a Range of Basis Sets[a]

$\mathrm{WW}_{\mathrm{planar}}$

	basis set	Morokuma	ind dipole MOC	QU+CL QMMMMOC	CL+QU QMMM MOC	mean abs QMMM MOC
1	STO-3G	−0.8	−2.7	**−1.2**	+0.1	0.7
2	3-21G	−1.0	−4.5	**−0.1**	**+0.4**	**0.3**
3	6-31++G	−4.4	−5.5	**+0.5**	**+2.5**	**1.5**
4	6-31G*	−2.6	−4.2	**−0.4**	**+0.8**	**0.6**
5	cc-pVDZ	−2.4	−3.5	**−3.5**	**+0.8**	**2.2**
6	aug-cc-pVDZ	−5.1	**−1.2**	−1.6	+2.8	2.2
7	6-311G**	−3.0	−3.6	**−0.1**	**+1.2**	**0.7**
8	DGTZVP	−3.6	−3.5	**+0.4**	**+1.6**	**1.0**
9	6-311++G**	−4.0	−3.2	**−2.3**	**+2.1**	**2.2**
10	6-311G(2df,2pd)	−3.5	−2.4	**−2.5**	**+1.4**	**2.0**
11	Sadlej pVTZ	−6.9	**+0.3**	+3.6	+4.4	4.0
12	6-311++G(2d,2p)	−4.4	−2.0	**−1.6**	**+2.3**	**2.0**
13	6-311++G(3df,3pd)	−5.4	**−1.1**	+2.2	+3.0	2.6
14	aug-cc-pVTZ	−8.1	**+1.5**	+4.8	+5.5	5.2

$\mathrm{WW}_{\mathrm{perp}}$

	basis set	Morokuma	ind dipole MOC	QU+CL MOC	CL+QU MOC	mean abs QMMM MOC
1	STO-3G	−0.2	−2.3	−0.3	−0.1	0.2
2	3-21G	−1.0	−4.5	**−0.1**	**+0.4**	**0.3**
3	6-31++G	−5.2	**−3.0**	+3.6	+3.9	3.8
4	6-31G*	−1.9	−4.2	**+0.6**	**+0.9**	**0.8**
5	cc-pVDZ	−2.1	−3.3	**+0.7**	**+0.8**	**0.8**
6	aug-cc-pVDZ	−7.2	**+0.3**	+5.2	+5.1	5.2
7	6-311G**	−3.1	−2.9	**+1.7**	**+1.8**	**1.8**
8	DGTZVP	−3.2	−3.4	**+1.7**	**+2.0**	**1.9**
9	6-311++G**	−6.2	**−0.7**	+4.4	+4.5	4.5
10	6-311G(2df,2pd)	−4.1	**−1.6**	+2.5	+2.3	2.4
11	Sadlej pVTZ	−10.2	**+3.2**	+8.3	+8.3	8.3
12	6-311++G(2d,2p)	−7.1	**+0.1**	+5.2	+5.1	5.2
13	6-311++G(3df,3pd)	−8.7	**+1.6**	+6.8	+6.8	6.8
14	aug-cc-pVTZ	−13.5	**+6.5**	+11.5	+11.3	11.4

[a] The MOC value that is generally lower (and therefore most consistent with the Morokuma energy decomposition value) for each system (i.e., induced dipoles or induced charges) and basis set is in bold type. Note that a negative MOC corresponds to an overestimate in the magnitude of polarization, and a positive MOC corresponds to an underestimate in the magnitude of polarization. QU+CL refers to the QMMM system where the water donating a hydrogen bond is modeled QM, and CL+QU refers to the system where the water that accepts a hydrogen bond is QM. The final column gives the mean of the absolute MOC of the two QMMM columns, QU+CL and CL+QU. All MOC values are given in kJ mol^{-1}.

at two levels. The first is to include polarization at the induced charge level, because this gives a consistent treatment of polarization for a range of moderately sized basis sets, even for the difficult case of geometries perpendicular to planar groups, as in $\mathrm{WW}_{\mathrm{perp}}$. The second level is to include polarization at the induced dipole level, and this is appropriate for very large basis set calculations. The induced dipole approach is therefore more accurate and this is in line with the use of multiple diffuse functions to accurately model polarization within quantum chemical calculations. However, within QM/MM calculations where the focus is naturally on the QM region, it would not be appropriate to couple a more accurate treatment of polarization (via induced dipoles) in the less important MM region with a moderate treatment of polarization in the more important QM region (via moderate sized basis set). The alternative of a moderate treatment of polarization in the less important MM region (e.g., through induced charges) with a full treatment of polarization in the more important QM region (through use of an appropriate diffuse basis set) may be acceptable but is not within the spirit of a consistent model chemistry.

Within wholly classical calculations, it is common practice to parametrize against quantum chemical calculations;[6] steps to include polarization in classical simulations should take into account the level of polarization inherent in the quantum chemical methods used in the parametrization, particularly as it is usually the electrostatics and not the polarization that have the dominant effect.

An approach for including induced dipoles within QM/MM calculations has been developed by van Duijnen,[44] but the induced charge scheme is more straightforward to implement. The induced charge scheme is only one of many alternatives to the generally accepted induced dipole approach, and other schemes have been successfully used by many authors, as discussed in ref 15. Nevertheless, as polarization is used more routinely, whether in QM/MM calculations or in classical simulations, consideration should be given to the appropriate model chemistry.

Conclusions

The primary conclusion from the water dimer calculations, despite unfavorable geometries for some water dimer orientations, is that within a specified model chemistry, the induced charge approach is consistent with medium size basis set calculations whereas the induced dipole approach is only consistent with large basis set calculations. This result is highly relevant to the concept of QM/MM model chemistries, because the introduction of polarization using an inappropriate scheme could lead to considerable imbalances in the relative magnitude of polarization within different domains of the calculations. The ease of implementation and interpretation of induced charges is a secondary benefit that may be useful in the interpretation of QM/MM calculations on large systems, which will of necessity need to be carried out using moderately sized basis sets.

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Supporting Information Available: Coordinates of water geometries; Morokuma (E_{pol}QM) polarization energy for a water dimer in optimized and perpendicular orientations calculated using a range of basis sets; population and ensemble measure of consistency values, for the neglect, QMMM (induced charge), and induced dipole methods, modeled using a range of basis sets. This material is available free of charge via the Internet at http://pubs.acs.org.

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