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The Application of the Effective Fragment Potential Method to Molecular Anion Solvation: A Study of Ten Oxyanion−Water Clusters, $A^-(H_2O)_{1-4}$

G. N. Merrill*

2155 29th Avenue, San Francisco, California 94116

S. P. Webb

Advanced Biomedical Computing Center, SAIC-Frederick, National Cancer Institute at Frederick,
P.O. Box B, Frederick, Maryland 21702

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The performance of the effective fragment potential (EFP) method, a quantum mechanical-molecular mechanical (QM-MM) method, to reproduce fully quantum mechanical results has been investigated. The enthalpies of hydration for 10 oxyanions (ClO_4^-, HSO_4^-, NO_3^-, $H_2PO_4^-$, HCO_3^-, HCO_2^-, SO_4^{2-}, HPO_4^{2-}, CO_3^{2-}, and PO_4^{3-}) by one to four water molecules were studied. For monohydrate systems exhibiting small to moderate amounts of charge transfer (ClO_4^-, HSO_4^-, NO_3^-, $H_2PO_4^-$, HCO_3^-, and HCO_2^-), the EFP method reproduces Hartree−Fock (HF) differential enthalpies of hydration remarkably well (mean difference = −0.1 and standard deviation = 0.9 kcal/mol). The EFP and HF calculations also successfully reproduce the available experimental data (EFP: mean difference = 2.0 and standard deviation = 0.8 kcal/mol; HF: mean difference = 1.8 and standard deviation = 1.0 kcal/mol). MP2 calculations show only a slight improvement in agreement with experiment over the HF calculations, indicating a small electron correlation effect. For the high charge-transfer monohydrate systems (SO_4^{2-}, HPO_4^{2-}, CO_3^{2-}, and PO_4^{3-}), the EFP method is less successful in reproducing HF differential enthalpies of hydration. The agreement between EFP and HF results improves, however, with the number of water molecules. These results suggest reduced variational space (RVS) analysis can be used to predict which systems may pose (charge transfer) problems for the EFP method.

I. Introduction

Molecular anions play key roles in countless chemical and biochemical reactions and processes. They are ubiquitous in biochemistry,[1] where, for instance, phosphates are the primary "energy currency" of living organisms. A number of molecular anions are also of great industrial importance,[2] an obvious example being nitrate fertilizers. Environmental concerns too surround many molecular anions,[3] notably eutrophication of lakes and rivers by nitrates and phosphates and contamination of groundwater by perchlorate. The reactivity of these anions is strongly affected by hydration, and many of the above chemical processes occur in water. It is, therefore, crucial to understand in detail the fundamental nature of molecular anion interactions with water if these processes are to be properly understood.

One way to gain insight into anion−water interactions at the molecular level is through computational chemistry. Molecular anions have complex charge distributions, and, therefore, a quantum mechanical description is usually essential. Inclusion of hydration effects in quantum mechanical calculations can be achieved with continuum models[4] or through inclusion of discrete water molecules[5] in the calculation. Continuum models fail to provide detailed information on solute−water interactions. While a discrete approach may be more suitable for anions in this respect, an obvious disadvantage is the large increase in cost associated with including water molecules in the electronic structure calculation. A quantum mechanical-molecular mechanical (QM-MM) approach[6] avoids this added cost by dividing the chemical system into quantum mechanical and classical regions, i.e., a QM description of the molecular anion and a MM description of the water molecules.

One such QM-MM method is the effective fragment potential (EFP) method developed by Gordon and co-workers.[7] The EFP method was designed to reproduce a given level of electronic structure theory. For example, Hartree−Fock (HF),[7a,b] multiconfigurational self-consistent field (MCSCF),[8] or density functional theory (DFT)[9] can be used to describe the quantum mechanical region, while a corresponding molecular mechanics potential is used to represent the classical region. The molecular mechanics potential interacts with the quantum region through one-electron integral perturbations to the Hamiltonian, which account for electrostatic, polarization, and exchange repulsion/charge-transfer effects.

The EFP method has successfully reproduced all ab initio results for a variety of chemical systems,[10] including a number of charged or zwitterionic systems,[11] even though the method was originally designed for use with neutral systems. These promising results notwithstanding, the most rigorous way to determine the EFP method's reliability regarding charged systems is through systematic benchmarking. We have previously carried out two such benchmarking studies: one on cation−water clusters,[12] $M(H_2O)_{1-6}$, where M is Li^+, Na^+, K^+, Mg^{2+}, and Ca^{2+}; and one on anion−water clusters,[13] $A^-(H_2O)_{1-6}$, where A is OH^-, F^-, SH^-, Cl^-, and Br^-. These studies showed

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* Address correspondence to this author.

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that the EFP method reliably reproduces all ab initio differential enthalpies of hydration for the ions studied, provided the degree of charge transfer in the system is not too great.

While the applicability of the EFP method to atomic anions has been demonstrated,[12,13] its performance with regard to the more complicated charge distributions of molecular anions has not been thoroughly investigated. To this end, the present study examines the EFP method's performance in describing the hydration of 10 molecular anions (ClO_4^-, HSO_4^-, NO_3^-, $H_2PO_4^-$, HCO_3^-, HCO_2^-, SO_4^{2-}, HPO_4^{2-}, CO_3^{2-}, and PO_4^{3-}) with up to 4 water molecules. The benchmarking of the EFP method for these molecular anions will facilitate the future application of the EFP method to many important chemical systems. For example, given the prevalence of the carboxylate group in biochemistry, an accurate description of this group's interaction with water is essential to a fundamental understanding of many biochemical processes (e.g., the structure and reactivity of proteins).

The performance of the EFP method (restricted Hartree−Fock (RHF) anions and EFP water molecules) is evaluated by comparison to electronic structure calculations, in which all atoms were treated quantum mechanically with the Hartree−Fock method. In addition, all ab initio second-order perturbation theory single-point energies are examined to assess electron correlation effects. Comparison to experiment is also made where data are available.[14]

We note that there are a number of computational studies in the literature dealing with (molecular) anion−water clusters.[15] Wang et al.[14e] studied $NO_3^-(H_2O)_{1-6}$ using density functional theory and large basis sets, while Waterland et al.,[15g] Shen et al.,[15c] and Howell et al.[15a] carried out Hartree−Fock calculations on $NO_3^-(H_2O)_{1-3}$. Pye and Rudolph[15h] have examined $SO_4^{2-}(H_2O)_{1-6}$ using second-order perturbation theory and a polarized double-ζ basis set. Yang et al.[15i] studied $SO_4^{2-}(H_2O)_{1-6}$ using density functional theory and a polarized triple-ζ basis set. Masamura[15f] has investigated $HCO_3^-(H_2O)_{1-8}$, and Gao et al.[15b] studied the $HCO_3^-H_2O$ system at various levels of theory. Finally, studies on $H_2PO_4^-(H_2O)_{1-3}$ were carried out by Wu et al.[15e] and Ma et al.[15d] at various levels of theory. Given that the main aim of this study is to establish the applicability of the EFP method to describe the hydration of molecular anions, we do not discuss these previous computational studies in detail. We do, however, point out several discrepancies with our present work.[16−18]

II. Methods

Two sets of calculations were carried out. In the first set, all water molecules were computed ab initio. In the second set, only the anions were treated ab initio, while the water molecules were modeled via effective fragment potentials (EFP). All structures were fully optimized (maximum gradient $\leq$ 0.012 kcal/mol Å and RMS gradient $\leq$ 0.004 kcal/mol Å) at the restricted Hartree−Fock (RHF) level of theory with the double split-valence 6-31G basis set of Pople and co-workers[19] to which sets of d- and p-polarization functions[20] were added to heavy and hydrogen atoms, respectively. As the present study involves anions, sets of sp- and s-diffuse functions[21] were also added to heavy and hydrogen atoms, respectively. This basis set will be referred to as "6-31++G(d,p)".

To verify that all optimized structures corresponded to minima, their associated Hessian matrixes were also computed at the RHF/6-31++G(d,p) level of theory. These calculations were performed analytically for all the ab initio structures and numerically with double differencing for the effective fragment potential ones. These matrixes permitted zero-point energy (ZPE) corrections to be computed. These ZPEs were scaled by an empirical factor of 0.9135 to compensate for the known overestimation of vibrational frequencies calculated at the RHF level of theory with polarized, double-ζ quality basis sets.[22]

Electrostatic/exchange (ESEX), polarization (POL), charge transfer (CT), and basis set superposition error (BSSE) energies for the RHF/6-31++G(d,p) optimized anion-monohydrates were determined by using the reduced variational space (RVS) energy decomposition scheme.[23]

To include the effects of dynamic electron correlation, second-order Møller−Plesset (MP2) single-point energy[24] calculations were performed upon the RHF optimized structures. Only the valence electrons were subjected to the perturbation, i.e., the frozen-core (fc) approximation was used.[25]

In the interest of clarity, the following nomenclature has been adopted when referring to the above levels of theory: HF $\equiv$ RHF/6-31++G(d,p); MP2 $\equiv$ MP2(fc)/6-31++G(d,p)//RHF/6-31++G(d,p); and EFP $\equiv$ EFP/6-31++G(d,p). All calculations were carried out with the GAMESS program.[26]

III. Results and Discussion

Illustrations of the anion−water clusters are given in Figure 1. Only the lowest energy species have been presented along with their point groups. It should be noted that symmetry constraints cannot be imposed in the current implementation of the effective fragment potential method (EFP), i.e., all structures belong to the C_1 point group. The more symmetric EFP structures have, nevertheless, been labeled with the point group they most closely resemble. As the effective fragment potential method makes use of a fixed internal geometry, only hydrogen bond distances have been compared. A statistical summary comparing the EFP and Hartree−Fock (HF) geometries can be found in Table 1. To the best of our knowledge, no experimental structural data are available for comparison.

Two types of hydrogen bonding have been analyzed. The first is between the anion and water molecules ($A^-\cdots H_2O$), while the second is between the water molecules themselves ($H_2O\cdots H_2O$). The EFP clusters evince slightly longer hydrogen bonds between the anions and the water molecules than their HF counterparts (mean difference = 0.08 Å and standard deviation = 0.06 Å). This trend is reversed for the hydrogen bonds between the water molecules (mean difference = −0.03 Å and standard deviation = 0.05 Å). Excluding the high charge-transfer species (SO_4^{2-}, HPO_4^{2-}, CO_3^{2-}, and PO_4^{3-}, vide infra) results in improved agreement between the EFP and HF structures with respect to the hydrogen bonds between the anions and water molecules (mean difference = 0.05 Å and standard deviation = 0.04 Å), while the agreement is essentially unchanged for the water−water hydrogen bonds.

As proposed in our earlier papers on small cation−water and anion−water clusters,[12,13] reduced variational space (RVS) analysis may be used to screen for systems with significant degrees of charge transfer, which may present problems for the current implementation of the effective fragment potential method. Such an RVS analysis was performed at the Hartree−Fock level of theory for the monohydrate−anion clusters. The results from this analysis are presented in Table 2, where the total interaction energy (Total) has been broken down into electrostatic/exchange (ESEX), polarization (POL), charge transfer (CT), and basis set superposition error (BSSE) components. The entries have been ordered in terms of their charge-transfer components, from smallest (ClO_4^-, CT = −0.6 kcal/mol) to largest (PO_4^{3-}, CT = −6.4 kcal/mol). A number of

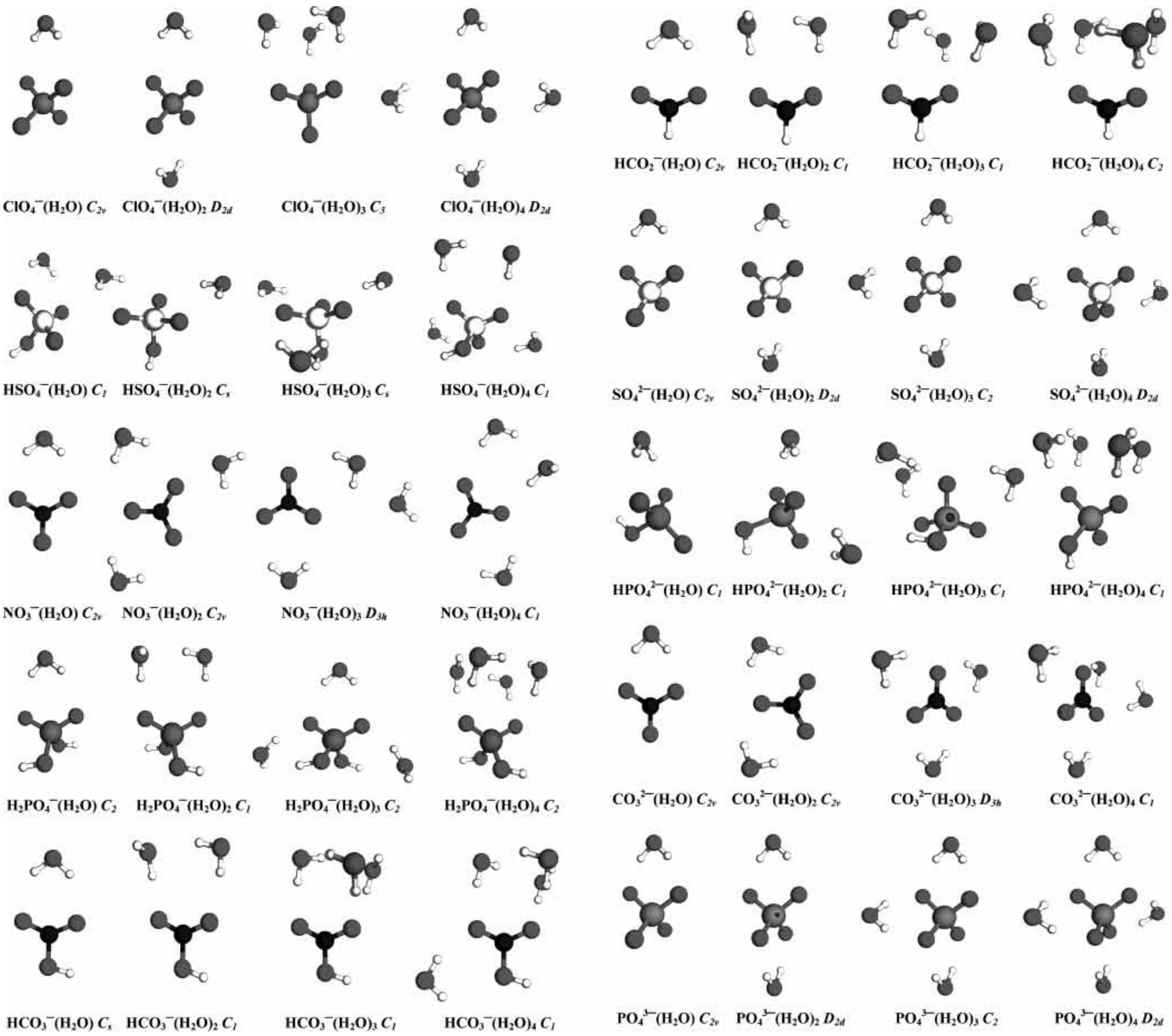

Figure 1. Illustrations of the anion−water clusters.

TABLE 1: Statistical Comparison of Hydrogen Bonding in Effective Fragment Potential (EFP) and Hartree−Fock (HF) Anion−Water Clusters[a]

	Δ(all species)		Δ(low charge-transfer species)[a]	
	$A^-\cdots H_2O$	$H_2O\cdots H_2O$	$A^-\cdots H_2O$	$H_2O\cdots H_2O$
mean	0.08	−0.03	0.05	−0.03
std dev	0.06	0.05	0.04	0.05
n	90	22	53	20

[a] Distances in Å. $A^-\cdots H_2O$: hydrogen bond between anion and water molecule. $H_2O\cdots H_2O$: hydrogen bond between water molecules. $\Delta = r_{EFP} - r_{HF}$. [b] Low charge-transfer species: ClO_4^-; HSO_4^-; NO_3^-; $H_2PO_4^-$; HCO_3^-; and HCO_2^-.

observations can be readily made. First, the electrostatic/exchange component dominates the interaction. It is only when multiply charged anions are considered that the next largest component (polarization) becomes significant. Second, basis set superposition error is rather modest for the monohydrate anions described by the 6-31++G(d,p) basis set, averaging only −0.6 kcal/mol.

On the basis of our earlier work with the OH^-H_2O cluster,[13] where charge transfer amounted to −8.7 kcal/mol, the EFP description of the CO_3^{2-} (CT = −4.5 kcal/mol) and PO_4^{3-} (CT = −6.4 kcal/mol) monohydrate clusters may be suspect. These two species do indeed have differential enthalpies of hydration that differ most from those determined at the HF level of theory (Δ = EFP − HF: $\Delta(CO_3^{2-}) = 5.3$ and $\Delta(PO_4^{3-}) = 8.1$ kcal/

TABLE 2: Reduced Variational Space (RVS) Energy Decomposition Performed at the RHF/6-31++G(d,p) Level of Theory for the $A^-(H_2O)_1$ Clusters[a]**aTotal = Electrostatic/Exchange (ESEX) + Polarization (POL) + Charge Transfer (CT) + Basis Set Superposition Error (BSSE). All Energies in Kcal/Mol**

$A(H_2O)_1$	ESEX	POL	CT	BSSE	total
ClO_4^-	−9.5	−1.3	−0.6	−0.5	−11.9
HSO_4^-	−11.2	−1.7	−0.8	−0.5	−14.2
NO_3^-	−11.8	−2.0	−0.9	−0.4	−15.1
$H_2PO_4^-$	−12.7	−2.1	−1.0	−0.5	−16.3
HCO_3^-	−13.8	−2.6	−1.2	−0.4	−18.0
HCO_2^-	−14.3	−2.9	−1.4	−0.4	−19.0
SO_4^{2-}	−20.8	−5.3	−2.2	−0.6	−28.9
HPO_4^{2-}	−22.2	−6.3	−2.9	−0.7	−32.1
CO_3^{2-}	−24.0	−8.6	−4.5	−0.6	−37.7
PO_4^{3-}	−30.2	−12.8	−6.4	−0.9	−50.3

[a] Total = electrostatic/exchange (ESEX) + polarization (POL) + charge transfer (CT) + basis set superposition error (BSSE). All energies in kcal/mol.

mol). The other multiply charged anions, SO_4^{2-} (CT = −2.2 kcal/mol) and HPO_4^{2-} (CT = −2.9 kcal/mol), possess the next largest Δ values: $\Delta(SO_4^{2-}) = 2.9$ kcal/mol and $\Delta(HPO_4^{2-}) = 3.3$ kcal/mol. The remaining six monohydrate anions all havecharge transfers of −1.4 kcal/mol or less and Δ values of 1.1 kcal/mol or less. It appears, therefore, that RVS analysis can serve as an effective diagnostic tool in screening species that may not be well described by the current implementation of the EFP method. In lieu of such an analysis,[27] caution should be exercised when modeling species with high energy highest occupied molecular orbitals (HOMOs).

Table 3 lists the differential enthalpies of hydration for the 10 anions for one to four water molecules (eq 1).

$$A(H_2O)_{n-1} + H_2O \rightarrow A(H_2O)_n \quad (n = 1-4) \qquad (1)$$

where A = ClO_4^-, HSO_4^-, NO_3^-, $H_2PO_4^-$, HCO_3^-, HCO_2^-, SO_4^{2-}, HPO_4^{2-}, CO_3^{2-}, and PO_4^{3-}. Where experimental data are available, it has been included as well. It should be noted, however, that these experimental values correspond to enthalpies at 298 K, whereas the computed ones are for 0 K. In our previous study on anion hydration,[13] however, we showed that temperature effects are small, allowing a meaningful comparison between experimental values determined at 298 K and computed values at 0 K. For each of the computed enthalpies, the structure with the lowest enthalpy was used. Often a number of low-energy clusters of a given size were found, usually within 1 to 2 kcal/mol of the value reported in Table 3. No averaging has been employed, as exhaustive conformational searches were not performed for the largest clusters ($n = 4$). We believe, however, that the reported structures are representative of the global minima. The focus of the present investigation was, moreover, on the ability of the EFP method to reproduce HF results.

As the effective fragment potential method was designed to reproduce results obtained at the Hartree−Fock level of theory, a comparison of the EFP and HF differential enthalpies of hydration was made. For the 40 reactions studied, a mean difference of only 1.1 kcal/mol and a standard deviation of 2.1 kcal/mol were found. These values improve further if the high charge transfer species (SO_4^{2-}, HPO_4^{2-}, CO_3^{2-}, and PO_4^{3-}) are excluded: mean difference = −0.1 and standard deviation = 0.9 kcal/mol. These results clearly demonstrate that the EFP method successfully reproduces the HF differential enthalpies of hydration. A closer look at the low charge transfer species (ClO_4^-, HSO_4^-, NO_3^-, $H_2PO_4^-$, HCO_3^-, and HCO_2^-) reveals that the largest absolute difference is only 2.6 kcal/mol ($H_2PO_4^-$, $n = 4$), and all but 4 of the 24 differences are 1 kcal/mol or less. Focusing on the high charge transfer species, the differences decrease with the addition of water molecules for the SO_4^{2-}, CO_3^{2-}, HPO_4^-, and PO_4^{3-} anions. Once the third water molecule has been added, the differences for these four anions approach those seen for the low charge transfer anions. These results clearly demonstrate that the EFP method reproduces the HF differential enthalpies of hydration very well. This is true even for the high charge transfer cases, provided more than two or three water molecules are present.

TABLE 3: Differential Enthalpies of Hydration ($\Delta\Delta_rH°$) at 0 K (in kcal/mol)[a]

n	expt	EFP	Δ_{Expt}	HF	Δ_{Expt}	MP2	Δ_{Expt}	Δ_{Calc}
$ClO_4^-(H_2O)_{n-1} + H_2O \rightarrow ClO_4^-(H_2O)_n$								
1	−11.8[b]	−9.4	2.4	−9.7	2.1	−11.7	0.1	0.2
2		−8.8		−8.8		−10.6		0.0
3		−9.4		−8.2		−12.2		−1.2
4		−5.5		−6.2		−5.8		0.7
$HSO_4^-(H_2O)_{n-1} + H_2O \rightarrow HSO_4^-(H_2O)_n$								
1	−12.9[b]	−11.1	1.8	−11.6	1.3	−13.4	−0.5	0.4
2	−11.7[b]	−10.3	1.4	−10.4	1.3	−12.2	−0.5	0.1
3		−9.3		−9.3		−12.0		0.0
4		−9.5		−7.9		−9.1		−1.5
$NO_3^-(H_2O)_{n-1} + H_2O \rightarrow NO_3^-(H_2O)_n$								
1	−14.1[b]	−11.7	2.4	−12.4	1.7	−14.6	−0.5	0.7
2	−12.2[b]	−10.7	1.5	−11.0	1.2	−13.0	−0.8	0.4
3	−10.9[b]	−9.7	1.2	−9.9	1.0	−11.7	−0.8	0.1
4		−7.4		−7.0		−9.0		−0.4
$H_2PO_4^-(H_2O)_{n-1} + H_2O \rightarrow H_2PO_4^-(H_2O)_n$								
1	−14.0[c]	−13.0	1.0	−13.4	0.6	−15.2	−1.2	0.4
2	−12.3[c]	−10.7	1.6	−11.0	1.3	−13.0	−0.7	0.3
3		−9.4		−10.2		−13.6		0.8
4		−12.8		−10.2		−13.1		−2.6
$HCO_3^-(H_2O)_{n-1} + H_2O \rightarrow HCO_3^-(H_2O)_n$								
1	−15.7[d]	−13.8	1.9	−14.8	0.9	−16.7	−1.0	1.0
2	−14.9[d]	−10.9	4.0	−11.0	3.9	−12.9	2.0	0.0
3	−13.6[d]	−11.2	2.4	−10.3	3.3	−13.3	0.3	−0.8
4	−13.4[d]	−10.7	2.7	−10.2	3.2	−11.9	1.5	−0.5
$HCO_2^-(H_2O)_{n-1} + H_2O \rightarrow HCO_2^-(H_2O)_n$								
1	−16.2[b]	−14.3	1.9	−15.4	0.8	−17.6	−1.4	1.1
2	−13.8[b]	−11.3	2.5	−11.4	2.4	−13.3	0.5	0.1
3	−12.1[b]	−11.5	0.6	−10.7	1.4	−13.5	−1.4	−0.8
4		−10.9		−10.2		−12.6		−0.7
$SO_4^{2-}(H_2O)_{n-1} + H_2O \rightarrow SO_4^{2-}(H_2O)_n$								
1		−21.7		−24.5		−27.6		2.9
2		−20.6		−22.6		−25.3		2.1
3		−19.0		−20.2		−22.9		1.1
4		−18.0		−18.5		−21.0		0.6
$HPO_4^{2-}(H_2O)_{n-1} + H_2O \rightarrow HPO_4^{2-}(H_2O)_n$								
1		−23.6		−26.9		−29.7		3.3
2		−22.3		−24.4		−26.9		2.1
3		−21.0		−22.3		−24.7		1.3
4		−16.8		−16.9		−19.6		0.1
$CO_3^{2-}(H_2O)_{n-1} + H_2O \rightarrow CO_3^{2-}(H_2O)_n$								
1		−26.1		−31.4		−35.1		5.3
2		−24.6		−28.3		−31.2		3.6
3		−23.3		−25.6		−28.0		2.3
4		−18.3		−18.1		−21.2		−0.2
$PO_4^{3-}(H_2O)_{n-1} + H_2O \rightarrow PO_4^{3-}(H_2O)_n$								
1		−34.7		−42.8		−46.3		8.1
2		−33.5		−39.7		−42.7		6.2
3		−31.5		−35.3		−38.4		3.8
4		−30.2		−32.9		−35.8		2.7
totals								
mean			2.0		1.8		−0.3	1.1 (−0.1)[d]
std dev			0.8		1.0		1.0	2.1 (0.9)[d]
n			15		15		15	40 (24)[d]

[a] Δ_{Expt} = calculated value − experimental value. Δ_{Calc} = EFP Value − HF Value. EFP ≡ EFP/6-31++G(d,p); HF ≡ HF/6-31++G(d,p); and MP2 ≡ MP2/6-31++G(d,p)//HF/6-31++G(d,p). See text for details. [b] Reference 14b. [c] Reference 14c. [d] Reference 14a. [e] Low charge-transfer species: ClO_4^-; HSO_4^-; NO_3^-; $H_2PO_4^-$; HCO_3^-; and HCO_2^-.

Experimental differential enthalpies of hydration are available for 15 of the reactions investigated. As it is experimentally difficult to study multiply charged ions, all of the experimental enthalpies involve singly charged (and low charge transfer) species. A mean error with respect to experiment of only 1.8 kcal/mol and a standard deviation of 1.0 kcal/mol were found at the HF level, and all clusters were found to be underbound. Given the uncertainties associated with the experimental measurements (typically ±1 kcal/mol), the HF method does an excellent job in reproducing experiment. Likewise, the EFP method also reproduces the experimental values well: mean error = 2.0 kcal/mol and standard deviation = 0.8 kcal/mol. It should be noted that the Møller−Plesset (MP2) level of theory performs best in reproducing the experimental differential enthalpies of hydration. For the 15 reactions examined, a mean

TABLE 4: Reduced Variational Space (RVS) Analysis and Differential Enthalpies of Hydration ($\Delta\Delta_r H°$) at 0 K (in kcal/mol) for Methoxide and *tert*-Butoxide[a]

$A(H_2O)_1$	ESEX	POL	CT	BSSE	total
$CH_3O^{-\,b}$	−8.6	−8.6	−6.0	−0.5	−23.7
$(CH_3)_3CO^{-\,b}$	−8.6	−7.3	−4.8	−0.4	−21.1

n	expt	EFP	Δ_{Expt}	HF	Δ_{Expt}	MP2	Δ_{Expt}	Δ_{Calc}
				$CH_3O^-(H_2O)_{n-1} + H_2O \rightarrow CH_3O^-(H_2O)_n$				
1	$-23.9^{c,d}$	−16.3	7.6	−20.0	3.9	−22.8	1.1	3.7
2	$-19.2^{c,d}$	−15.4	3.8	-17.3^{b}	1.9	-19.8^{b}	−0.6	1.9
3	$-14.8^{c,d}$	−14.9	−0.1	−14.3	0.5	−16.0	−1.2	−0.6
4	$-11.0^{c,d}$	−12.2	−1.2	-11.3^{b}	−0.3	-13.6^{b}	−2.6	−0.9
5		−9.3		−8.7		−12.2		−0.6
6		−9.3		−9.2		−10.6		−0.1
				$(CH_3)_3CO^-(H_2O)_{n-1} + H_2O \rightarrow (CH_3)_3CO^-(H_2O)_n$				
1	-23.4^{e}	−15.5	7.9	−18.1	−5.3	−20.0	3.4	2.6
2		−14.8		-15.7^{b}		-17.8^{b}		0.9
3		−14.4		−13.7		−16.0		−0.7
4		−11.6		-9.8^{b}		-12.9^{b}		−1.8
5		−8.8		−8.7		−11.0		−0.1
6		−9.3		−8.1		−11.6		−1.2

[a] Total = electrostatic/exchange (ESEX) + polarization (POL) + charge transfer (CT) + basis set superposition error (BSSE). Δ_{Expt} = calculated value − experimental value. Δ_{Calc} = EFP value − HF value. EFP ≡ EFP/6-31++G(d,p); HF ≡ HF/6-31++G(d,p); and MP2 ≡ MP2/6-311++G(d,p)//HF/6-31++G(d,p). Unless otherwise noted, all $\Delta\Delta_r H°$ values were from Damrauer.[11d] See text for details. [b] This work. [c] Meot-Ner, M.; Sieck, L. W. *J. Phys. Chem.* **1986**, *90*, 6687. [d] Meot-Ner, M. *J. Am. Chem. Soc.* **1986**, *108*, 6189. [e] Meot-Ner, M.; Sieck, L. W. *J. Am. Chem. Soc.* **1986**, *108*, 7525.

error of only −0.3 kcal/mol and a standard deviation of 1.0 kcal/mol were calculated. While consideration of dynamic electron correlation effects leads to slightly improved agreement with the experiment, the HF level provides differential enthalpies of hydration of sufficiently high accuracy to permit the quantitative investigation of anion hydration. A high degree of confidence can also be assigned to the EFP results given the method's ability to reproduce those obtained at the HF level of theory.

Damrauer[11d] has carried out a series of calculations on the methoxide and *tert*-butoxide water clusters with the effective fragment potential and with ab initio (Hartree−Fock and second-order Møller−Plesset) levels of theory. Differential enthalpies of hydration, derived from his work, are given in Table 4. We have performed RVS analyses on the monohydrate clusters, and these results are also listed in Table 4. Both clusters exhibit significant degrees of charge transfer: $CH_3O^-H_2O$, CT = −6.0 kcal/mol; and $(CH_3)_3CO^-H_2O$, CT = −4.8 kcal/mol. It is not too surprising that the EFP and HF differential enthalpies differ from one another ($CH_3O^-H_2O$, Δ = 3.7 kcal/mol and $(CH_3)_3CO^-H_2O$, Δ = 2.6 kcal/mol) and their experimental counterparts. The differences with respect to experiment improve, however, with increasing cluster size.

The total enthalpies of hydration for the ten anions for one to four water molecules (eq 2) can be found in Table S1 of the Supporting Information, where A = ClO_4^-, HSO_4^-, NO_3^-,

$$A^- + nH_2O \rightarrow A^-(H_2O)_n \quad (n = 1-4) \qquad (2)$$

$H_2PO_4^-$, HCO_3^-, HCO_2^-, SO_4^{2-}, HPO_4^{2-}, CO_3^{2-}, and PO_4^{3-}. Total enthalpies of hydration are far more difficult to predict than their differential counterparts. Comparing the forty reactions studied at the EFP and HF levels of theory reveals a mean difference of 3.8 kcal/mol and a standard deviation of 5.3 kcal/mol. If the four high charge transfer species are excluded, the mean difference and standard deviation drop precipitously to 0.4 and 0.7 kcal/mol, respectively, for the remaining twenty-four reactions. Examining the individual anion series does not show any particular trends for the low charge transfer species, but the differences increase significantly with the number of water molecules for those anions exhibiting high charge transfer. It appears, therefore, that the EFP method is capable of reproducing HF total enthalpies of hydration for systems exhibiting small degrees of charge transfer.

For the high charge transfer species, agreement between the EFP and HF levels of theory is poorest, especially for the addition of the first few water molecules. By the time the third or fourth water molecule is added, the increase in error becomes quite small, but the total error is still large. This suggests that interactions between these anions and the first few water molecules are not properly described by the EFP method.

With regards to reproduction of the 15 experimental total enthalpies of hydration, the MP2 level performs best (mean error = −0.6 kcal/mol and standard deviation = 1.4 kcal/mol). There is no apparent systematic trend for the MP2 results. The HF and EFP results are more marginal: HF, mean error = 3.4 kcal/mol and standard deviation = 2.9 kcal/mol; and EFP, mean error = 4.1 kcal/mol and standard deviation = 2.7 kcal/mol. All of the HF and EFP clusters are underbound. Similar results are obtained from the data of Damrauer[11d] for the methoxide and *tert*-butoxide anions.

These results suggest that dynamic electron correlation is needed to accurately reproduce experimental total enthalpies of hydration for the present anions. Even though the EFP level of theory reproduces the HF results for the low charge transfer species, the HF level is incapable of reproducing experimental total enthalpies of hydration. These results further emphasize the importance of selecting the appropriate level of theory.

IV. Conclusions

The differential and total enthalpies of hydration of ten molecular anions for one to four water molecules and their structures have been investigated with the effective fragment potential (EFP) method. The results have been compared with those obtained at the Hartree−Fock (HF) and Møller−Plesset (MP2) levels of theory and with experiment.

Hydrogen bond distances were also compared for the EFP and HF structures. The two levels of theory are in fairly good agreement with one another, with the EFP clusters leading to somewhat longer bonds between the anions and water molecules and slightly shorter bonds between the water molecules themselves.

For anions exhibiting little to modest amounts of charge transfer, the EFP method successfully reproduces the HF differential enthalpies of hydration, and both levels of theory reproduce the available experimental data well. For anions evincing large amounts of charge transfer, the EFP and HF differential enthalpies are in poorer agreement, especially for the addition of the first couple of water molecules. Comparison of the MP2 differential enthalpies of hydration with experiment shows only a slight improvement over the EFP and HF results, indicating a small dynamic electron correlation effect. The EFP method provides, therefore, a reliable way of determining differential enthalpies of hydration for molecular anions exhibiting small amounts of charge transfer.

The HF total enthalpies of hydration are closely reproduced at the EFP level of theory for the low charge transfer species. Comparison with available experimental data reveals that the two levels of theory are not as successful as they were in reproducing the experimental differential enthalpies of hydration. The MP2 results are in substantially better agreement with experiment, indicating dynamic electron correlation is more important in calculating total enthalpies of hydration.

On the basis of this and previous studies,[12,13] reduced variational space (RVS) analysis can serve as a diagnostic tool in predicting which systems may pose (charge transfer) problems for the EFP method. The EFP method appears to be capable of accommodating small to modest amounts of charge transfer (CT $\leq$ 2.0 kcal/mol). For systems with larger degrees of charge transfer, the EFP method should be exercised with more caution, especially for clusters with only a few water molecules.

It is important to ensure that the level of theory being reproduced by the EFP method adequately describes the system under study. For systems requiring a description of dynamic electron correlation, the use of recently developed, correlation-consistent effective fragment potentials should be considered (e.g., DFT).[9]

To date the EFP method lacks an explicit charge-transfer term. In the current implementations, exchange repulsion/charge-transfer interactions are fit to the water dimer potential by a single term. As shown here and elsewhere,[12,13] this description is not adequate for systems experiencing large amounts of charge transfer. A future direction in the development of the EFP method should be the investigation of explicit charge-transfer and exchange-repulsion terms.

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Supporting Information Available: Two tables (S1 and S2) containing total enthalpies of hydration. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Voet, D.; Voet, J. G. *Biochemistry*, 2nd ed.; John Wiley and Sons: New York, 1995.

(2) Chenier, P. J. *Survey of Industrial Chemistry*; John Wiley and Sons: New York, 1986.

(3) (a) Manahan, S. E. *Fundamentals of Environmental Chemistry*, 2nd ed.; Lewis Publishers: Boca Raton, FL, 2001. (b) The topical nature of this subject can be seen in the following cover story: Hogue, C. *Chem. Eng. News* **2003**, August 18th.

(4) Cramer, C. J.; Truhlar, D. G. *Reviews in Computational Chemistry*; Boyd, D. B., Lipkowitz, K. B., Eds.; VCH: New York, 1995; Vol. 6.

(5) We know of no general review of the supermolecular approach. The results of this method are scattered over dozens of articles. An example of one such study is the following: Jensen, J. H.; Gordon, M. S. *J. Am. Chem. Soc.* **1995**, *117*, 8159.

(6) Gao, J. *Reviews in Computational Chemistry*; Boyd, D. B., Lipkowitz, K. B., Eds.; VCH: New York, 1996; Vol. 7.

(7) (a) Jensen, J. H.; Day, P. N.; Gordon, M. S.; Basch, H.; Cohen, D.; Garmer, D. R.; Krauss, M.; Stevens, W. J. *Modeling the Hydrogen Bond*; Smith, D. A., Ed.; ACS Symp. Ser. 569; 1994. (b) Day, P. N.; Jensen, J. H.; Gordon, M. S.; Webb, S. P.; Stevens, W. J.; Krauss, M.; Garmer, D.; Basch, H.; Cohen, D. *J. Chem. Phys.* **1996**, *105*, 1968. (c) Gordon, M. S.; Freitag, M. A.; Bandyopadhyay, P.; Kairys, V.; Jensen, J. H.; Stevens, W. J. *J. Phys. Chem. A* **2001**, *105*, 293.

(8) (a) Krauss, M.; Webb, S. P. *J. Chem. Phys.* **1997**, *107*, 5771. (b) Grigorenko, B. L.; Nemukhin, A. V.; Topol, I. A.; Burt, S. K. *J. Phys. Chem. A* **2002**, *106*, 10663.

(9) Adamovic, I.; Freitag, M. A.; Gordon, M. S. *J. Chem. Phys.* **2003**, *118*, 6725.

(10) (a) Chen, W.; Gordon, M. S. *J. Chem. Phys.* **1996**, *105*, 11081. (b) Merrill, G. N.; Gordon, M. S. *J. Phys. Chem. A* **1998**, *102*, 2650. (c) Day, P. N.; Pachter, R.; Gordon, M. S.; Merrill, G. N. *J. Chem. Phys.* **2000**, *112*, 2063. (d) Kairys V.; Jensen J. H. *J. Phys. Chem. A* **2000**, *104*, 6656. (e) Grigorenko, B. L.; Nemukhin, A. V.; Grigorenko, A. V.; Topol, I. A.; Burt, S. K. *J. Mol. Struct. (THEOCHEM)* **2002**, *581*, 167. (f) Nemukhin, A. V.; Topol, I. A.; Grigorenko, B. L.; Burt, S. K. *J. Chem. Phys. B* **2002**, *106*, 1734. (g) Nemukhin A. V.; Grigorenko B. L.; Topol I. A.; Burt S. K. *J. Comput. Chem.* **2003**, *24*, 1410.

(11) (a) Day, P. N.; Pachter, R. *J. Chem. Phys.* **1997**, *107*, 2990. (b) Webb, S. P.; Gordon, M. S. *J. Phys. Chem. A* **1999**, *103*, 1265. (c) Gordon, M. S.; Petersen, C. P. *J. Phys. Chem. A* **1999**, *103*, 4162. (d) Damrauer, R. *J. Am. Chem. Soc.* **2000**, *122*, 6739. (e) Bandyopadhyay, P.; Gordon M. S. *J. Chem. Phys.* **2000**, *113*, 1104. (f) Nemukhin, A. V.; Topol, I. A.; Grigorenko, B. L.; Burt, S. K. *J. Phys. Chem. B* **2002**, *106*, 1734.

(12) Merrill, G. N.; Webb, S. P.; Bivin, D. B. *J. Phys. Chem. A* **2003**, *107*, 386.

(13) Merrill, G. N.; Webb, S. P. *J. Phys. Chem. A* **2003**, *107*, 7852.

(14) (a) Keesee, R. G.; Lee, N.; Castleman, A. W., Jr. *J. Am. Chem. Soc.* **1979**, *101*, 2599. (b) Blades, A. T.; Klassen, J. S.; Kebarle, P. *J. Am. Chem. Soc.* **1995**, *117*, 10563. (c) Blades, A. T.; Ho, Y.; Kebarle, P. *J. Am. Chem. Soc.* **1996**, *118*, 196. (d) Wang, X.-B.; Nicholas, J. B.; Wang, L.-S. *J. Chem. Phys.* **2000**, *113*, 10837. (e) Wang, X.-B.; Yang, X.; Wang, L.-S.; Nicholas, J. B. *J. Chem. Phys.* **2002**, *116*, 561.

(15) (a) Howell, J. M.; Sapse, A. M.; Singman, E.; Synder, G. *J. Phys. Chem.* **1982**, *86*, 2345. (b) Gao, J.; Garner, D. S.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1986**, *108*, 4784. (c) Shen, M.; Xie, Y.; Schaefer, H. F., III. *J. Chem. Phys.* **1990**, *95*, 3379. (d) Ma, B.; Xie, Y.; Shen, M.; Schleyer, P. v. R.; Schaefer, H. F., III *J. Am. Chem. Soc.* **1993**, *115*, 11169. (e) Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1993**, *115*, 11997. (f) Masamura, M. *J. Phys. Chem.* **1993**, *97*, 3157. (g) Waterland, M. R.; Stockwell, D.; Kelley, A. M. *J. Chem. Phys.* **2001**, *114*, 6249. (h) Pye, C. C.; Rudolph, W. W. *J. Phys. Chem. A* **2001**, *105*, 905. (i)Yang, X.; Wang, X.-B.; Wang, L.-S. *J. Phys. Chem. A* **2002**, *106*, 7607.

(16) Ma and co-workers (ref 15d) have performed a series of calculations on the mono- and dihydrates of $H_2PO_4^-$. They calculated enthalpies (298 K) of −13.5 and −8.4 kcal/mol for the addition of one and two water molecules, respectively, at the Hartree−Fock level of theory with a polarized, double-ζ basis set to which diffuse functions have been added. Their value for the addition of the first water is in good agreement with our calculated value (HF = −13.4 kcal/mol) and that of experiment (−14.0 kcal/mol). Their value for the addition of the second water differs, however, from our value (HF = −11.0 kcal/mol) and that of experiment (−12.3 kcal/mol). It should be noted that the C_2 structure used in their calculations is 3.1 kcal/mol higher in energy than our C_1 structure at the HF/6-31++G(d,p) level of theory. This would account for a large part of the apparent discrepancy between their computed results and that of experiment. Wu and Houk (ref 15e) found C_2 structures for both the mono- and dihydrated $H_2PO_4^-$ clusters at the HF/6-31+G(d) level. They report enthalpies of hydration (0 K) of −13.5 and −10.7 kcal/mol for the addition of one and two water molecules, respectively.

(17) Masamura (ref 15f) investigated the hydration of formate with up to eight water molecules at the RHF/6-31++G(d) level of theory. Only the mono- and dihydrated clusters were fully optimized, and only high symmetry conformations were examined. C_s and C_{2v} structures were reported for the mono- and dihydrated clusters. Differential internal energies were calculated for the first and second additions of water molecules: $\Delta\Delta_rE°(0\rightarrow1) = -15.5$ kcal/mol and $\Delta\Delta_rE°(1\rightarrow2) = -14.2$ kcal/mol. These values compare fairly well with the experimental enthalpies: $\Delta\Delta_rH°(0\rightarrow1) = -16.2$ kcal/mol and $\Delta\Delta_rH°(1\rightarrow2) = -13.8$ kcal/mol. It must be noted, however, that neither of these species correspond to global minima at the HF/6-31++G(d,p) level of theory. At this level, the C_s monohydrate cluster is 2.8 kcal/mol higher in energy than the C_{2v} structure, and the C_{2v} dihydrate cluster is 1.6 kcal/mol higher in energy than the C_1 structure. When zero-point energies are included, the agreement with experiment worsens: $\Delta\Delta_rH°(0\rightarrow1) = -13.2$ and $\Delta\Delta_rH°(1\rightarrow2) = -11.9$ kcal/mol. The agreement of Masamura's results with experiment is clearly fortuitous. The above conclusion is also consistent with the earlier work of Gao et al. (ref 15b) on the $HCO_2^-H_2O$ cluster.

(18) An experimental and computational study has been performed by Waterland and co-workers (ref 15g) on the mono- and dihydrated nitrate clusters. They identified two low-energy species for both clusters at the HF/6-311++G(d,p) level of theory. The C_{2v} monohydrate was found to be 2.0 kcal/mol lower in energy than the C_s one. A C_s dihydrate structure, based upon the C_{2v} monohydrate, was found to be 2.0 kcal/mol lower in energy than the analogous C_s structure derived from the C_s monohydrate cluster. The monohydrate results are consistent with those we obtained. Our results differ, however, from theirs for the dihydrated clusters. At the HF/6-31++G(d,p) level, the C_{2v} structure is 1.9 kcal/mol lower in energy than the C_s one. We also located a C_{2v} structure at their level of theory (HF/6-311++G(d,p)) that was 1.8 kcal/mol lower in energy than their C_s structure. Our results are consistent with those obtained by Howell et al. (ref 15a). A minor discrepancy exists between our results and those of Wang et al. (ref 14e) for the $NO_3^-H_2O$ cluster. They report that at the B3LYP/aug-cc-pVTZ and MP2/aug-cc-pVTZ levels of theory the minimum energy structure has C_s symmetry, while the C_{2v} structure is a transition state. Our C_{2v} structure is a minimum. The origin of this difference appears to reside

in the use of correlated structures. Their results for the $NO_3^-(H_2O)_{2-4}$ structures are consistent with ours. There is, moreover, good agreement between their differential enthalpies of hydration and ours.

(19) (a) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724. (b) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257. (c) Francl, M. M.; Pietro, W. J.; Hehre, W. J.; Binkley, J. S.; Gordon, M. S.; DeFrees, D. J.; Pople, J. A. *J. Chem. Phys.* **1982**, *77*, 3654.

(20) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213.

(21) (a) Frisch, M. J.; Pople, J. A.; Binkley, J. S. *Theor. Chim. Acta* **1984**, *80*, 3265. (b) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. v. R. *J. Comput. Chem.* **1983**, *4*, 294. (c) Spitznagel, G. W. *Diplomarbeit*; Erlangen, 1982.

(22) (a) Pople, J. A.; Scott, A. P.; Wong, M. W.; Radom, L. *Isr. J. Chem.* **1993**, *33*, 345. (b) Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502.

(23) (a) Stevens, W. J.; Fink, W. H. *Chem. Phys. Lett.* **1987**, *139*, 15. (b) Chen, W.; Gordon, M. S. *J. Phys. Chem.* **1996**, *100*, 14316. (c) Cammi, R.; Bonaccorsi, R.; Tomasi, J. *Theo. Chim. Acta* **1985**, *68*, 271.

(24) Fletcher, G. D.; Rendell, A. P.; Sherwood, P. *Mol. Phys.* **1997**, *91*, 431.

(25) (a) Saunders, W. H., Jr. *J. Phys. Org. Chem.* **1994**, *7*, 268. (b) Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502.

(26) Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Gordon, M. S.; Nguyen, K. A.; Su, S.; Windus, T. L.; Elbert, S. T.; Montgomery, J.; Dupuis, M. *J. Comput. Chem.* **1993**, *14*, 1347.

(27) Other types of analysis, which can determine the extent of charge transfer, may also be useful in this regard. One reviewer suggested that Natural Bond Order (NBO) analysis may be similarly effective. We have, however, only validated our conclusions with the RVS method.