Using Locally Dense Basis Sets for the Determination of Molecular Properties

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The applicability of locally dense basis sets (LDBS) to the accurate computational determination of gas-phase bond dissociation enthalpies, substituent effects in para-substituted phenols, solvation energies, hydrogen-bond strengths, activation energies, and proton and electron affinities is examined. A general molecular partitioning scheme is presented and found to reproduce most properties to within 1 kcal/mol of the balanced basis set treatment. Slight modifications of the suggested partitioning scheme was required for the accurate determination of proton and electron affinities. Comparisons and implications of the locally dense basis set approach to current computational methods are presented. The present results suggest that the LDBS approach offers a computationally efficient alternative to large, balanced-basis set calculations of certain molecular properties and is a viable approach for large-molecule property computation.

I. Introduction

The quantum-mechanical treatment of large molecular systems has traditionally been a difficult task owing to poor scaling and/or hardware limitations. However, recent developments in ab initio methods,[1,2] density functional approaches,[3] and hybrid MM/QM techniques[4] have been remarkably successful in obtaining molecular energies for very large systems. In many cases, these procedures take advantage of the local behavior in chemical systems to greatly reduce the complexity of the computational problems associated with large-molecule calculations.

Along with the development of procedures to extend the size of molecules that can be treated using quantum-mechanical methods, there has also been substantial interest in increasing the accuracy of properties calculated using standard (i.e., small-molecule) methods. The refinement of the G1 procedure[5] into G2 and G3,[6,7] for example, now allows for the determination of heats of formation for ground state molecules containing up to 10 heavy atoms to within about 1 kcal/mol of the experimental value. In addition, density functional (DFT) techniques[8] continue to evolve and are able to produce increasingly accurate molecular properties at a fraction of the computational effort of traditional ab initio calculations. These have been used to accurately evaluate important molecular properties such as bond dissociation enthalpies.[9]

In a recent study,[9] we focused on the problems associated with the accurate computational determination of bond dissociation enthalpies (BDEs) specifically applied to antioxidants.[10] Searching for an approach that can compute X−H BDEs to within 1 kcal/mol of experiment, we developed a series of models similar in nature to the G2 method. By coupling semiempirical or low-level ab initio geometry and frequency determinations with large basis set, single-point DFT energies, we were able to determine very accurate BDEs, and proton and electron affinities. These in turn were used to study substituent effects, gas-phase acidities, and one-electron reduction potentials for a representative set of X−H species. Furthermore, by replacing the computationally intensive correlation energy evaluation inherent in a G2-type calculation with a single-point DFT calculation, these models are able to treat larger molecules than standard ab initio correlation approaches. Continuing in this direction, we have endeavored to extend one of these models such that accurate bond dissociation enthalpies could be applied to molecules as large as 100 atoms using locally dense basis sets (LDBS). In fact, we have recently shown that the O−H BDE in α-tocopherol (vitamin E, 81 atoms) can be accurately and efficiently obtained using an LDBS approach.[11]

The idea behind the use of locally dense basis sets is similar to that in applied MM/QM calculations: by applying one's understanding of a molecular system, the region of chemical interest in a species can be identified and treated in more detail than the rest of the molecule. Similarly, the LDBS approach involves identifying the part of a molecule where, for example, a bond is being broken (for a BDE calculation) and using a large basis set to describe the atoms involved in that region. The rest of the molecule is treated with a smaller basis set or series of basis sets. By applying such an approach, DFT (or any conventional correlation) calculations can be performed on much shorter time scales than fully balanced (large) basis calculations. Additionally, the use of LDBS can alleviate other problems such as convergence difficulties and hardware limitations. Of course, applying an attenuated basis set on a large portion of the molecule results in electronic energies that are significantly higher than those obtained using a larger balanced basis set. However, if reactant and product species are treated in a consistent manner, these energy differences may cancel. In this respect, the LDBS approach is similar to the use of split-valence basis sets[12] or effective core potentials[13] where core electrons are poorly treated but error cancellation results in the ability to determine properties relatively accurately.

The locally dense basis set approach was first systematically applied by Huber and Diel[14] to the calculation of Hartree−Fock electric field gradients.[39] These authors found that gradients computed using larger, balanced basis sets could be accurately reproduced with attenuated bases on parts of the molecular systems under investigation. Chesnut et al.[15] later applied LDBS to calculate NMR chemical shifts in large molecules. The Chesnut group applied large basis sets to the NMR chro-

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mophores while using smaller basis sets for the rest of the molecule. By showing that chemical shifts could be accurately determined in this way, and at a fraction of the computational expense, Chesnut's approach has become a standard procedure in the NMR community.[16] Other groups have used the LDBS approach to calculate different properties. Orozco and Luque[17] have applied locally dense basis sets to compute molecular electrostatic potentials and Pardo et al.[18] applied them to model proton transfer in biological systems. In addition, the use of locally dense basis sets for the determination of molecular geometries, dipole moments, and other properties was explored by Jensen and Gordon.[19] More recently, Chesnut and Byrd found that the LDBS approach could be used to accurately estimate correlation energies at the QCISD level.[20] By using an expression similar to that for the counterpoise correction, the authors were able to determine QCISD energies to within about 4 kcal/mol of the larger, balanced basis results but at a fraction (usually two or three) of the computer time. The success of these studies in rapidly and accurately determining a variety of molecular properties clearly indicates that *the application of local chemistry concepts could be useful in improving the efficiency with which computational studies are performed.*

The purpose of the present paper is to study the applicability of locally dense basis sets to a variety of important chemical applications including the determination of bond dissociation enthalpies, solvation enthalpies, hydrogen-bond strengths, activation energies, and proton and electron affinities. We begin by presenting a partitioning scheme and corresponding basis sets with which a variety of molecules are treated. We conclude the study with a discussion of the applicability of the LDBS approach to other methodologies.

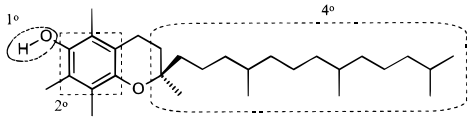
II. Computational Details

A. Suggested Partitioning Schemes and Basis Set Assignments. To apply the locally dense basis set approach to an arbitrary system, one must first decide how to partition the molecule(s) of interest. At first glance, the partitioning of a molecules and subsequent regional basis set assignments may seem critical. However, Chesnut[15,20] and others[19] have already shown that the LDBS approach is quite insensitive to both basis set and partitioning. That is, *the LDBS method is robust*. These findings indicate that partitioning methods used in the LDBS approach are much less critical than one might expect, in particular for the determination of properties such as bond dissociation enthalpies (BDE). For a BDE, equivalent partitioning is applied to both the neutral parent compound and the radical species. Thus, inadequacies in the descriptions of the molecules are the same and significant error cancellation results in an accurate BDE.

Rather than present exhaustive tests on large permutations of basis sets and partitioning schemes, an approach that has proven to be quite successful in previous applications[9,11] will be outlined. In certain sections, some molecules are subjected to intentionally drastic partitioning in order to illustrate the robust nature of the LDBS approach.

In general, our partitioning method is based on a functional group approach. By using functional groups, parsing a molecule into fragments of varying significance can be performed intuitively and consistently. The first step to partitioning a molecule is to identify the center(s) at which the chemistry is occurring. The O−H bond dissociation enthalpy of the vitamin E molecule was recently computed using the LDBS approach. This molecule, illustrated in Scheme 1, will serve as an example for partitioning. For a bond dissociation enthalpy determination

SCHEME 1: An Example of the Application of a Locally Dense Basis Set Partitioning Scheme Used for the O−H Bond Dissociation Enthalpy Calculation for α-Tocopherol (Vitamin E)



[a] The groups that are not circled belong to the tertiary partition. Basis sets for each partition are as indicated in the text.

the atoms directly involved in the chemical bond are those which must be best described. We identify this portion of the molecule (the O−H atoms) as primary (1°). In previous work,[11] we have shown that X-H BDEs could be predicted to within 1 kcal/mol of experiment using the B3LYP density functional with a 6-311+G(2d,2p) basis set.[9] This set of functions is therefore chosen to represent the 1° region(s). Typically the primary region of the molecule will be quite small, making this large basis set assignment tractable. In addition to a σ-bond linking the primary and secondary regions, it is possible that other strong interactions between partitions may be present. In these cases, conjugative or hydrogen-bonding interactions will be shown to be unaffected by partitioning in terms of their contribution to the properties of interest.

Functional groups bonded to the primary region are labeled secondary (2°). In the present example, the benzene ring in vitamin E is considered secondary and is assigned a 6-311+G-(d) basis set.The tertiary region (3°) is defined to contain those functional groups or parts thereof which are directly bonded to the secondary region. For vitamin E, this includes the methyl groups bonded to the benzene ring in addtion to the oxygen atom at the para position relative to the hydroxyl group. These groups are assigned a 6-31G(d) basis set. The remaining groups in vitamin E are defined as quaternary and are assigned a minimal, STO-3G basis set.

It will be shown in later sections that the outlined partitioning scheme is not necessarily appropriate for all cases. However, it will also be shown that LDBS determined properties converge quite quickly to the balanced basis set values indicating the general utility of the approach.

B. Methods. For all molecules presented in this study, optimum geometries and vibration frequencies were determined using the AM1 method[21] as implemented in the Spartan 5.0 package.[22] Vibrational frequencies, used for the evaluation of zero-point energies (ZPEs) and vibrational enthalpies, were scaled by a factor of 0.973, which we have previously found to reproduce ZPEs determined at higher levels of theory.[9]

Electronic energies were computed using locally dense basis sets and compared with balanced basis set values where, in all cases, these values were determined using the largest basis set applied in the locally dense basis set treatment (i.e., the basis set applied to the primary region). The B3LYP density functional[23,24] was used to evaluate single-point energies unless otherwise specified. All calculations involving open-shell systems were treated within the restricted-open shell formalism (e.g., (RO)B3LYP). Molecular enthalpies, H°_{298}, were determined by taking the sum of the electronic and zero-point energies along with the appropriate enthalpic corrections. In all cases, the enthalpy of an isolated hydrogen atom is taken to be $H^\circ_{298} = -0.49764$ hartree.[9]

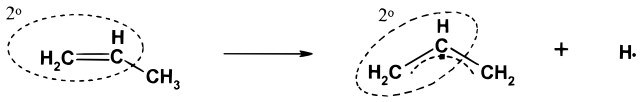
Solvation energies were determined by single-point energy calculations on gas-phase, AM1 optimized structures using the self-consistent isodensity polarized continuum model method.

TABLE 1: Calculated Bond Dissociation Enthalpies for Propene Using Locally Dense and Fully Balanced (FB) Basis Sets with Various Computational Methods[a]

	HF		B3LYP		MP2		CCSD	
secondary basis set	LDBS	FB	LDBS	FB	LDBS	FB	LDBS	FB
STO-3G	54.8	57.2	87.9	94.7	90.5	−23.4	85.5	81.8
6-31G(d)	57.1	56.3	86.8	87.1	90.4	83.2	85.2	78.1
6-31+G(d)	57.1	56.8	86.4	86.6	90.0	87.0	84.5	82.0
6-311+G(d)	57.3	57.2	86.8	86.8	90.2	88.3	84.8	83.4
6-311+G(2d,2p)	57.4	57.5	86.9	86.9	90.4	89.3	84.8	83.9
6-311++G(3df,3pd)	57.5		86.9		90.8		85.1	

[a] The molecule is divided into "primary"and "secondary" regions as in Scheme 2. In all cases, the primary basis set is 6-311++G(3df,3pd). Values are in kcal/mol. The experimental BDE is given in ref 26 as 88.2 ± 2.1 kcal/mol.

SCHEME 2: Partitioning for the Dissociation Reaction for Propene[a]



[a] The basis set for the circled region is varied while the remaining atoms are treated with a large basis set.

Spartan 5.0 was used to build and display molecules while Gaussian-94[25] was used for all electronic energy computations.

III. Results

A. Test Calculations on Propene. We begin by examining the applicability of the locally dense basis set approach to various computational procedures. By applying the LDBS approach to the calculation of the alkyl C−H bond dissociation enthalpy (BDE) in the propene molecule, we hope to be able to gauge its generally utility.

Propene represents a particularly challenging case for the LDBS approach for a number of reasons. The removal of an alkyl hydrogen results in the formation of a symmetric (C_{2v}) allyl radical. That is, since both ends of the radical are perfectly equivalent by symmetry, the application of different basis sets to the radical breaks this inherent symmetry.[40] Equivalently, the unpaired electron resides in a molecular orbital (MO) which is completely delocalized over the entire molecule. This MO is necessarily described in an unbalanced manner by the LDBS approach. Finally, central to the LDBS approach is the assumption that the property of interest is highly localized. Since propene is quite small, the nonlocal nature of the radical makes the assumption of a localized BDE questionable.

As described in the previous section, all geometries and frequencies for propene and its radical were determined using the AM1 method. Consequently, all BDE evaluations compare only the effects of changing basis sets of different portions of the molecule on the electronic energy for the bond-breaking process. The molecules were partitioned for LDBS treatment according to the Scheme 2.

The circled atoms, which are designated as "secondary", were treated with basis sets ranging from the minimal STO-3G to the largest split-valence 6-311++G(3df,3pd) basis while the remaining atoms (−CH_3) were described throughout by that largest basis set.

Table 1 contains the BDE results for breaking the alkyl C−H bond as a function of secondary basis set using the HF, B3LYP, MP2, and CCSD methods. Fully balanced (FB) results were obtained using the indicated secondary bases and are shown for comparison. One may immediately notice that despite the inherent difficulties associated with treating the propene dissociation process with unbalanced bases, predicted LDBS BDEs vary by less than 2.7 kcal/mol over all secondary basis sets and for all methods. On the other hand, the application of the indicated fully balanced basis sets produces BDEs which converge slowly from values in considerable disagreement with the large basis set BDEs. For example, the MP2/(FB)STO-3G bond dissociation enthalpy is predicted to be negative while the corresponding B3LYP result is about 8 kcal/mol higher than the value using the 6-311++G(3df,3pd) basis. It is interesting to note that the HF(FB)/STO-3G BDE is only a few tenths of a kcal/mol in error relative to the basis set limit for that method.

As expected, increasing the size of the secondary basis to 6-31G(d) greatly improves the BDEs when balanced basis sets are used. Balanced HF and B3LYP BDEs are calculated to be within about 1 kcal/mol of the large basis values while the CCSD and MP2 values are within 7 and 8 kcal/mol, respectively. The corresponding LDBS bond dissociation enthalpies appear to be essentially converged, with all LDBS BDEs being within 1 kcal/mol of the large basis set values for all four procedures. Further increases in the balanced basis set results in effectively converged BDEs using HF and B3LYP while those determined with the MP2 and CCSD methods only slowly approach their respective limiting values.

In summary, excluding the out-lying HF/STO-3G result, we find that *all LDBS bond dissociation enthalpies for propene are calculated to be within 1 kcal/mol of the fully balanced, largest basis set treatment at the HF, MP2, B3LYP, and CCSD levels.* Considering the system to which the LDBS approach is being applied, that is, the small size of the propene molecule, the loss of symmetry (with unbalanced basis set assignment), and the delocalization of the singly occupied molecular orbital, these findings are dramatic and encouraging. The results suggest that for bond dissociation enthalpies, *the locally dense basis set approach may be applied with any computational procedure*.

B. Substituent Effects in *Para*-Substituted Phenols. Having demonstrated, as have others[20] that LDBS can be used in conjunction with several different methods, we wish now to focus only on further applications of the locally dense basis set approach for the determination of chemical properties. For our subsequent studies, we choose the B3LYP[23,24] density functional method primarily because it has been previously shown to be capable of predicting accurate X−H bond energetics[9] to within 1 kcal/mol. Note that the propene BDE determined at using (RO)B3LYP with 6-311+G(2d,2p) basis sets (the basis set used to define primary regions in LDBS) was in exact agreement with the BDE determined using (RO)B3LYP/6-311++G-(3df,3pd). This technique was also shown (above) to give the best convergence to the fully balanced basis set BDE in propene. The B3LYP approach also offers the advantage of speed over other conventional computational procedures and does not directly rely on good quality virtual orbitals to obtain accurate correlation energies. The latter point may explain the findings of Chesnut and Byrd in their use of LDBS for correlation energy determination.

SCHEME 3: Partitioning Scheme and Basis Set Assignments for *Para*-substituted Phenols for O−H Bond Dissociation Calculations

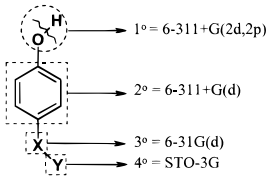


TABLE 2: O−H Bond Dissociation Enthalpies (Relative to Phenol) for *Para*-Substituted Phenols Using LDBS and Fully Balanced Basis Sets[a]

	basis			
X−Y substituent	LDBS	balanced	exptl 1[b]	exptl 2[b]
N-Me_2	−11.3	−10.1	−9.6	−14.1
NH_2	−9.4	−9.3	−12.6	−12.7
OH	−5.9	−5.9	−8.3	−8.0
O-Me	−6.7	−6.1	−5.3	−5.6
Me	−2.5	−2.6	−1.1	−2.1
Cl	1.4	1.5	0.4	−0.6
H	0	0	0	0
C−F_3	3.2	2.5	5.5	
C−N	1.7	2.3	4.4	4.7
N−O_2	4.2	4.5	4.5	6.0

[a] The calculated absolute BDES for phenol are 87.1 kcal/mol in both cases. Experimental values are shown for completeness. All tabulated values are in kcal/mol. [b] See ref 27. [c] See ref 28.

Para-substituted phenols are closely related to natural antioxidants (e.g., vitamin E) and have been well studied. In the creation of novel synthetic antioxidants, one of the design criteria is a low strength of the phenolic bond. This can be accomplished through the addition of one or more substituents to the benzyl ring. In this section, the substituent effects on the O−H BDE using the LDBS approach are determined and compared with results obtained with balanced basis sets.

Partitioning of and subsequent basis set assignment to the phenolic systems is performed as indicated in Scheme 3. The primary region is chosen to be the −OH moiety while the phenyl system (including hydrogen atoms) is taken to be secondary. Substituents in the *para*-position relative to the hydroxyl group are treated as entirely tertiary or both tertiary and quaternary depending on whether non-hydrogen atoms are bonded to the X atom. Normally one would treat the entire substituent group as a single partition but in the case of larger groups further subdivision may become a necessity. In this section, the result of performing such extreme partitioning is examined.

Table 2 contains the bond dissociation enthalpies (relative to phenol) for *para*-substituted phenols. The substituents were chosen so that a broad range of both electron-donating and -withdrawing groups were represented. Bond dissociation enthalpies calculated using the LDBS approach and with fully balanced, 6-311+G(2d,2p), basis sets are listed. For easier comparison, relative BDEs are tabulated and shown with available experimental values. Note that since the calculated absolute BDE for phenol is in excellent agreement with experiment (i.e., 87.3 (ref 10) vs 87.1 kcal/mol, both LDBS and FB), the agreement between calculated and experimental relative BDEs reflects the agreement between the corresponding absolute values.

The results in the table show that bond dissociation enthalpies are reproduced to with 1.2 kcal/mol of the fully balanced result using the LDBS approximation. The largest error appears in the dimethylaminophenol BDE and seems to be the result of assigning the methyl groups as quaternary. The LDBS relative bond dissociation enthalpy decreases to −10.5 kcal/mol when the methyl groups are represented as tertiary. The BDEs for the remaining para-susbstituted phenols which are also subjected to drastic partitioning do not show errors as large as that for dimethylaminophenol. That is, the predicted BDEs for cyano-, trifluoro, methoxy-, and nitrophenol are all found to be within about 0.6 kcal/mol of the respective balanced basis results. The remaining BDE values are predicted to within 0.5 kcal/mol.

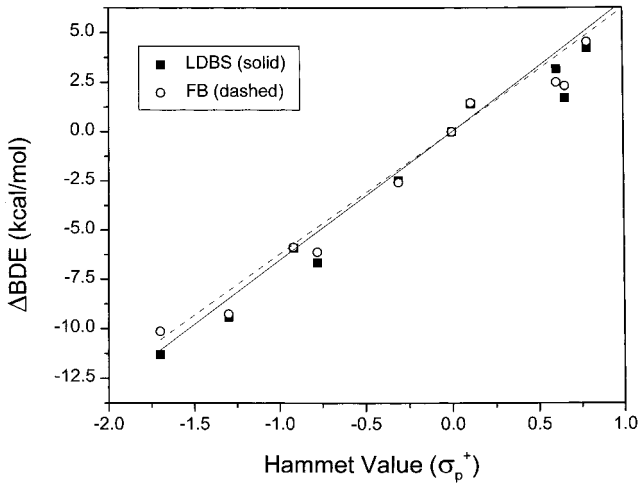


Figure 1. Gas-phase bond dissociation enthalpies (relative to phenol) for *para*-substituted phenols versus Hammett substituent parameter. See text for definitions.

The computational results shown in Table 2 are plotted in Figure 1 as a function of the Hammett σ_p^+ substituent parameter.[29] These parameters are used to correlate substituent effects with molecular properties and the resulting derived relationships are often useful in physical organic chemistry applications such as quantitative structure−activity relationship (QSAR) studies. The LDBS and balanced basis bond dissociation enthalpies are fitted by a least-squares procedure giving: BDE(LDBS) = $6.52\sigma_p^+$ and BDE(FB) = $6.21\sigma_p^+$. Both lines are seen to provide excellent fits to the data and are nearly indistinguishable from each other, as indicated by the slopes of the lines. The standard deviations are on the order of 1.1 kcal/mol and correlation coefficients close to 0.99. The slopes of the lines give so-called ρ^+ values that are 6.5 (LDBS) and 6.2 kcal/mol. The values compare quite well with an experimental value of 7.3 kcal/mol.[30] These findings indicate *that the locally dense basis set approach provides excellent agreement with balanced basis set and experimental substituent effects in substituted phenols. The LDBS relative and absolute bond dissociation enthalpies agree very well with both balanced basis and experimental values.* The plot of relative BDE against Hammett parameter illustrates that *minor errors resulting from LDBS use are inconsequential in the study of susbstituent effects on the BDEs of para-substituted phenols. These findings imply that the LDBS approach should prove useful in QSAR applications.*

The origin of the error cancelation in the *para*-substituted phenols is difficult to completely identify. We suspect that this cancelation is similar to that which occurs when split-valence basis sets are used in computational studies. In such cases, the poor treatment of the core results in higher energies than those which would be determined with a more detailed core basis set, but error cancellation results in relatively accurate properties. Efforts are currently underway in our laboratory to analytically demonstrate the origin of this error cancelation by representing the LDBS approach in a Feshbach projection operator formalism.[31]

TABLE 3: Gas-phase Dipole Moments, Solvation Energies, and Change in BDE Relative to Gas-phase for Two *Para*-Substituted Phenols Using Locally Dense Basis Sets (LDBS) and Fully Balanced (FB) Basis Sets

		dipole moment		solvation energy		
para-substituent	basis	neutral	radical	neutral	radical	ΔBDE
$-NMe_2$	FB	1.97	7.73	−7.4	−11.8	−4.5
	LDBS	2.97	8.92	−8.5	−13.6	−5.1
$-NO_2$	FB	5.35	0.77	−11.8	−10.0	+1.7
	LDBS	3.81	0.78	−9.2	−8.5	+0.6

[a] See text for partitioning details. Values are in debye and kcal/mol.

C. Solvation Energies and Bond Dissociation Enthalpies. The gas-phase BDEs computed using the LDBS approach were shown in the previous section III.B to accurately reproduce balanced basis set results. As previously discussed, the application of an unbalanced basis set to a molecule results in calculated electronic energies which disagree significantly from those found using a large balanced basis. Bond dissociation enthalpies are well reproduced because the errors associated with the energies almost completely cancel when energy differences are taken.

In addition to electronic energy, one would expect quantities such as dipole moment or other properties derived from the electronic distribution within a molecule to also be poorly predicted as a result of the unbalanced basis set treatment associated with LDBS. This is expected since energies tend to converge more rapidly than other properties derived from molecular wave functions. In this section, the effect that this unbalanced basis set treatment has on the computed solvation energy and BDE of dimethylaminophenol and nitrophenol is examined. The treatment of the phenol molecule is omitted since the LDBS and balanced basis sets used for this species are nearly identical (see Scheme 2). Consequently, the solvation results for phenols would be uninformative. The $-NMe_2$ and $-NO_2$ para-substituted phenols were chosen as the test molecules since these substituents have the largest effect on the BDE of phenol (see section III.B). Furthermore, the dipole moments for these molecules have the largest discrepancies (relative to balanced basis dipoles) of all the molecules listed in Table 2 indicating that LDBS electronic distributions are in considerable error relative to those predicted by the balanced basis calculations. These large dipole moment differences are expected since these substituents donate or withdraw electrons to the greatest extent. The solvent chosen for these studies is water (dielectric constant = 78.6).

Table 3 contains the dipole moments for the neutral and radical dimethylamino- and nitrophenol species using LDBS and balanced basis sets. For both molecules, the LDBS partitioning was performed as outline in Scheme 2.

The LDBS predicted dipole moments of neutral molecules are seen to be in considerable disagreement with those determined using balanced basis sets. Specifically, dipole moments are predicted to be in error by 51 and 29% for the neutral $-NMe_2$ and $-NO_2$ substituted phenols, respectively. The corresponding radical LDBS dipole moments are in error by 15 and 1%. These differences in dipole moments can be rationalized by considering the nature of the substituents and the basis sets applied to them. In the case of dimethylaminylphenol, the smaller (LDBS) bases representing this substituent result in less electronic density on the fragment relative to the balanced basis treatment. Consequently, the $-N(CH_3)_2$ group is less electron donating and the LDBS dipole moment is larger than that determined with the balanced basis. For the corresponding radical, the situation is reversed: the O atom on the phenoxyl moiety is strongly electron-withdrawing and stabilizes the excess electronic density from the under-described $-N(CH_3)_2$ group. As a result, the LDBS dipole moment for the dimethylaminylphenoxyl radical is larger than the balanced basis dipole. Similar arguments can be applied to nitrophenol and its radical.

Since the dipole moment is an indicator of the electronic distribution and solvation energies are dependent upon an accurate description of that distribution, one would expect solvation energies to be poorly predicted using the LDBS approach.

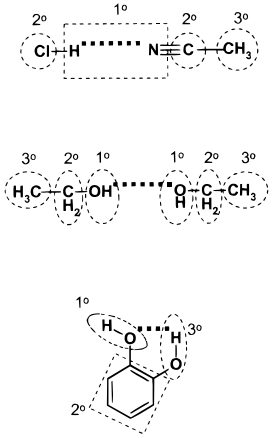
The data in Table 3 indicates that the skewed electronic distribution due to the application of locally dense basis sets does not significantly alter the solvation energies for the test compounds. For the neutral $-NMe_2$ substituted species, fully balanced and LDBS solvation energies differ by 1.1 kcal/mol despite the large error in predicted dipole. It is not unexpected to find that the LDBS solvent stabilization is higher than that predicted using a full basis given that the LDBS dipole is the larger of the two. Similar results are observed for the dimethylaminophenol radical: the dipole moment is predicted to be higher using the LDBS treatment and a correspondingly higher solvation stabilization is found. Differences between LDBS and FB solvation energies for the radical $-NMe_2$ species amount to 1.8 kcal/mol. For the dimethylaminophenol molecule, the LDBS treatment results in both the neutral and radical species being overly stabilized in water solvent. Consequently, LDBS errors in the solvation energies roughly cancel and give excellent ΔBDE results compared to the balanced basis findings. For this compound, the water solvent LDBS bond dissociation enthalpy predicted to be within 0.6 kcal/mol of the balanced basis result. This is a *smaller* difference than that found between the calculated gas-phase BDEs for this molecule.

For nitrophenol, similar results are obtained. For the neutral species, the LDBS dipole is predicted to be lower than that found using the balanced basis. Accordingly, a lower water solvent stabilization is observed for LDBS nitrophenol. It is interesting to note the perhaps odd result concerning the nitrophenoxyl radical; despite dipole moments that are essentially equivalent by balanced basis or LDBS treatments, the solvation energy differences using the two approaches are on the same order as those found for the neutral. Ultimately, the difference in solvation energies result in predicted increases in BDE that differ by 1.1 kcal/mol.

Considering that the magnitude of the water solvent stabilization of the test molecules and radicals is fairly small (i.e., 7−12 kcal/mol), the good agreement between LDBS and FB results is not too surprising despite the errors in the predicted dipole moments. It is therefore expected that, for solvents with dielectric constants smaller than water, the agreement between locally dense and balanced basis set solvation energies should improve. This must be the case given that the limiting dielectric of zero corresponds to the gas-phase results for which LDBS and FB BDEs have already been shown to be in excellent agreement.

On the basis of the present findings, we may state that (water) *solvation energies determined using the LDBS approach reproduce the balanced basis results to within 2.5 kcal/mol* for the test species. Furthermore, the *LDBS bond dissociation enthalpies for these water solvated species reproduce the balanced basis results to within 1.5 kcal/mol*. Results obtained using LDBS with solvents having lower dielectric constants than water are expected to be in better agreement with balanced basis set findings.

SCHEME 4: Partitioning Scheme Applied to Hydrogen Bonded Complexes[a]



[a] The basis set assignments are as suggested in section II.A of the text.

TABLE 4: Hydrogen Bond Strengths and Bond Dissociation Enthalpy for Three Compounds Using Locally Dense (LDBS) and Fully Balanced (FB) Basis Sets[a]

H-bonded system	LDBS	FB
$ClH\cdots NCCH_3$	5.6	5.7
$(C_2H_5OH)_2$	3.0	2.9
1,2-dihydroxybenzene	77.9	77.9

[a] For partitioning of the systems, see Scheme 4. All values are in kcal/mol.

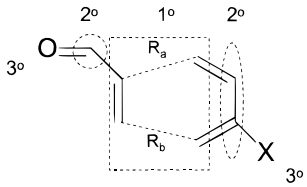
Given that solvation effects are most pronounced in water (compared to organic solvents) and given the large range in the dipole moments of the test species the present results indicate that the LDBS approach shows promise as an alternative to balanced basis set solvent calculations.

D. Hydrogen Bonding Interactions. Closely related to the discussion of solvation effects is hydrogen bonding. To accurately compute the effects of explicit solvent, hydrogen-bond (H-bond) interactions must be well modeled. In addition, the treatment of explicit water molecules (or other solvent molecules) for the determination of solvation effects results in a substantial increase in the number of molecules which must be treated. It is therefore of interest to explore the applicability of LDBS to the calculation of hydrogen-bond strengths.

The water dimer, normally the benchmark system for hydrogen-bond studies, is not treated here due to its small size. For $(H_2O)_2$, the suggested partitioning scheme would result in only primary atoms. Consequently, larger molecular systems are chosen to study the application of LDBS to H-bond systems. The systems examined are HCl−cyanomethane, the ethanol dimer, and 1,2-dihydroxybenzene. The latter molecule has an internal hydrogen bond that results in lowering the −OH BDE of one of the second hydroxyl group. This set of test systems is somewhat diverse and conclusions drawn from them should be general. The partitioning for these systems is shown in Scheme 4.

Calculated hydrogen bond strengths are shown in Table 4. For 1,2-dihydroxybenzene, the LDBS treatment of H-bonding is measured by computing the BDE of the primary −OH group. In effect, this BDE serves as a measure of the differences in the hydrogen bond strengths between the neutral and radical species of this system. The remaining hydrogen bond strengths are determined by the enthalpy difference between complexed and free molecules.

SCHEME 5: Partitioning Scheme Used for the Diels−Alder Reaction of Acrolein with 2-X-1,3-butadiene (X = methyl, *tert*-butyl)[a]



[a] Uncircled portions are tertiary. Basis sets assigned to the various regions are as indicated in section a of Methods. Dashed lines between carbons indicate the reacting centers.

As was done for *p*-cyanophenol in section III.B, the cyano group in cyanomethane was partitioned across the triple bond to test the effect of extreme partitioning on the predicted strength of the H-bond. Despite this partitioning, the LDBS predicted hydrogen bond strength for the hydrochloric acid−cyanomethane complex agrees to within 0.1 kcal/mol of the balanced basis result. Similar results are obtained for the ethanol dimer, where LDBS and FB hydrogen bond strengths are 3.0 and 2.9 kcal/mol, respectively. For 1,2-dihydroxybenzene, bond dissociation enthalpies using LDBS and FB approaches are in exact agreement, suggesting that the miniscule errors in H-bond strengths which occur as a result of using LDBS completely cancel.

These results suggest that *the LDBS approach can be applied to the determination of hydrogen bond strengths with little or no loss in accuracy*. This has positive implications for the use of LDBS in conjunction with explicit solvent, quantum mechanical studies.

E. Activation Energies. Activation energies for reactions are important chemical properties that can be difficult to compute. Often, the combination of two reactant molecules results in a system on which large-basis calculations cannot be performed due to time or hardware constraints. Recently, Svensson and co-workers devised the ONIOM scheme whereby a system is subdivided, capped, and treated using various levels of theory.[32] One set of systems they studied involved the Diels−Alder reaction of acrolein (propenal) with both 2-methyl-1,3-butadiene and 2-*tert*-butyl-1,3-butadiene. In this section, activation energies computed using the locally dense basis set approach are compared with the findings of Svensson et al. and balanced basis set treatments.

The partitioning of the reaction system was performed as indicated in Scheme 5. The partitioning method given in section II.A suggests that the methyl moieties of the *tert*-butyl group be treated as quaternary. However, we treat the *tert*-butyl group entirely as tertiary owing to obvious steric interactions with the reacting acrolein. For the systems, both the reactants and the transition state (TS) complexes were optimized using the AM1 method. Separations between the reacting carbons were found to be 2.22 and 2.04 Å for R_a and R_b, respectively (see Scheme 5). These distances can be compared with those obtained from ref 32 of 2.59 and 2.05 Å for R_a and R_b, respectively, using B3LYP/6-31G(d). At first glance, the large disagreement in R_a appears worrisome. However, preliminary (AM1) explorations of relative motion along this coordinate showed the potential to be very shallow. Furthermore, we are primarily interested in comparing LDBS and balanced basis results and not errors associated with the AM1 method. Errors associated with the

TABLE 5: Transition State Energies for the Reaction of Acrolein with 2-X-1,3-Butadiene where X = methyl and *tert*-Butyl[a]

method [ref]	E_a (X = *tert*-butyl)	E_a (X = methyl)
HF/6-31G(d) [32]	39.7	41.1
HF/6-31G(d)	39.9	42.0
B3LYP/6-31G(d) [32]	16.4	19.2
B3LYP/6-31G(d)	16.1	19.0
CCSD(T):MP2:MP2[b] [32]	16.9	19.6
B3LYP/6-311+G(2d,2p)	20.5	23.2
LDBS	19.7	22.7

[a] See text for LDBS partitioning. All values in kcal/mol. [b] Using 6-31G(d) basis sets.

use of the AM1 procedure will not change conclusions based on LDBS and FB comparisons.

Activation energies (E_a) are collected in Table 5. In order to further test the TS geometry findings with those of ref 32, we also present balanced basis 6-31G(d) energies at the HF and B3LYP levels. Hartree−Fock activation energies are shown to be in quite good agreement with those of the previous work, with *X* = *tert*-butyl and methyl values being within 0.2 and 0.9 kcal/mol, respectively, of those in ref 32. The results obtained using the B3LYP method are in even better agreement with both sets of activation energies, being within 0.3 kcal/mol of the results presented in ref 32. These findings would seem to confirm preliminary findings in this work of a very shallow potential along the R_a coordinate.

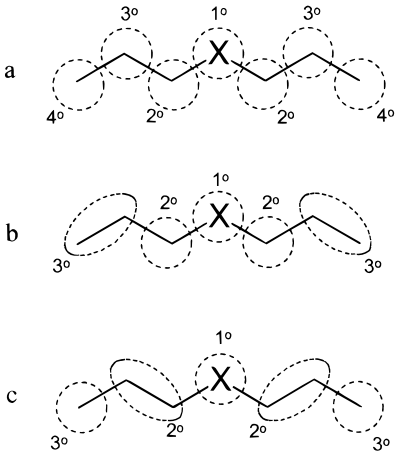
At the highest level of treatment (ONIOM(CCSD(T)/6-31G(d):MP2/6-31G(d):MP2/6-31G(d)), Svensson et al. find activation energies of 16.9 and 19.6 kcal/mol for X = *tert*-butyl and methyl, respectively.[32] The difference in activation energies ΔE_a is found to be 2.7 kcal/mol at that level. Using a 6-311+G(2d,2p) balanced basis set with the B3LYP functional, we find activation energies that are 3.6 kcal/mol higher than the ONIOM results for both transition states. The locally dense basis set results are in quite good agreement with the balanced basis findings with the former activation energies being 19.7 and 22.7 kcal/mol, for X = *tert*-butyl and methyl, respectively. The resulting ΔE_a value using LDBS is 3.0 kcal/mol, 0.3 kcal/mol higher than the balanced basis and ONIOM results.

In summary, the present findings indicate that *the LDBS approach successfully reproduced the fully balanced basis set results for activation energy calculations* on the acrolein + 2-methyl-1,3-butadiene and acrolein + 2-*tert*-butyl-1,3-butadiene systems. The present results were also found to agree quite well with those of Svensson et al. despite the use of different methods for determining geometries. The good agreement is expected given the similarities between the LDBS approach and the ONIOM method. Further comparisons between the LDBS approach and other methods will be present in a later section.

F. Proton Affinities. Proton attachment to a given species is usually associated with a lone pair of electrons. Since, under normal circumstances, lone pairs are highly localized on a single atom, one might expect the LDBS approach to be well suited to the calculation of proton affinities (PA). In this section, the computed proton affinities of dipropylamine, dipropyl ether, and dipropyl sulfide are examined with various partitioning schemes. It has been previously shown that B3LYP/6-311+G(2d,2p)/AM1/AM1 model calculations reproduce experimental proton affinities to within about 2 kcal/mol.[9]

The partitioning schemes for the dipropyl compounds are shown in Scheme 6. In all cases the central moieties (X = NH, O, S) are treated as primary (6-311+G(2d,2p)) while the

SCHEME 6: Partitioning Schemes Used for Dipropylamine, Dipropyl Ether, and Dipropyl Sulfide for Proton Affinity Calculations[a]



[a] In all cases, only the central X species (X = NH, O, S) is treated as primary. The remaining partitions are as indicated and basis sets are assigned as outlined in section II.A.

TABLE 6: Proton Affinities (0 K) Calculated Using the LDBS Approach with Various Partitioning Schemes (see Scheme 6)[a]

	partitioning scheme				
H_9C_3-X-C_3H_9 X =	*a*	*b*	*c*	FB	exptl [33]
NH	233.6	230.0	229.5	229.4	229.0
O	204.6	200.7	200.2	200.0	203.6
S	210.0	206.7	206.3	206.2	207.9

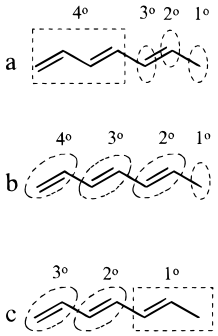
[a] Also shown are fully balanced (FB) basis set (6-311+G(2d,2p)) and experimental results. All values are in kcal/mol.

remaining carbon units fragments have variable assignments. As in the previous sections, geometries and frequencies are determined using the AM1 procedure. The zero Kelvin proton affinities calculated using the various partitions are collected in Table 6 with the balanced basis (6-311+G(2d,2p)) and experimental results.

A comparison of the proton affinities determined using the partitioning in Scheme 6a reveals that the values are consistently larger than the FB results by nearly 5 kcal/mol. This immediately suggests that the perturbation that arises with proton attachment is too great to be adequately modeled with a quaternary (STO-3G) partition on the terminal methyl groups. That is, proton affinity in these cases does not appear to be so well localized that our suggested partitioning scheme (section II.A and Scheme 6a) and basis set assignments can be used to accurately compute the property. Upon extension of the tertiary partition to include the $-CH_3$ groups (Scheme 6b), PA values overestimate the FB results by less than 0.7 kcal/mol in all cases. Increasing the secondary partition to include two $-CH_2-$ groups and leaving the terminal methyl groups as tertiary further improves PAs by about 0.5 kcal/mol, bringing them to within 0.2 kcal/mol of the FB results. The FB proton affinities are within about two kcal/mol of experiment for dipropylamine and dipropyl sulfide. The balanced basis PA for dipropyl ether is 3.6 kcal/mol, too low relative to the experimental value.

It is interesting to note that *differences* in the predicted PAs remain relatively constant for all three LDBS partitioning schemes. In other words, despite the overestimated PAs using partitioning Scheme 6a, the poor treatment appears to be roughly constant over three compounds. This implies that, through

SCHEME 7: Partitioning Schemes Used for Heptatrienyl for Electron Affinity Calculations[a]



[a] The basis set assignments for each partition are given in the text.

additional error cancellation, errors associated with inappropriate partitioning can be avoided and trends in PA may be accurately reproduced.

Overall, *the LDBS approach reproduces proton affinities for the dipropyl-substituted NH, O, and S atoms, predicting PAs to within 0.7 kcal/mol of the balanced basis set results.* However, it seems that the perturbation arising from proton attachment cannot be adequately reproduced with a quaternary partition on the terminal methyl groups in these compounds. A slight extension of the tertiary partition to encompass these terminal methyl groups was found to produce excellent PA results.

G. Electron Affinities. Electron affinities (EAs) are traditionally a difficult property to calculate. For accurate EAs, systems typically require large basis sets with diffuse functions. Since these requirements invariably result in calculations with convergence problems and/or excessive computer times, it is of interest to explore the applicability of the locally dense basis set approach to the determination of electron affinities. The test species chosen for this property are the heptatrienyl and *n*-pentylthio radicals. For the former species, conjugation over the entire length of the molecule represents an extreme test case for the LDBS approach.

In the case of proton affinities, the addition of H^+ resulted in a large enough change in the electronic distribution that our default partitioning scheme was inadequate (see section F above). In that case, however, proton attachment occurs at a highly localized center in the molecule. For electron attachment, it is expected that a greater degree of perturbation in the electronic density (becoming more diffuse and delocalized) is observed despite the fact that attachment occurs in an orbital with an unpaired electron. Consequently, calculated electron affinities determined using various partitioning schemes and basis sets are presented.

The partitioning schemes used for the heptatrienyl radical are shown in Scheme 7. The sizes of the partitions are varied, as is the tertiary basis set. Calculated electron affinities are listed in Table 7 with the full basis set and experimental[34] values of 28.9 and 29.3 kcal/mol, respectively.

The partitioning of the heptatrienyl radical using the method/basis sets suggested above (see section II.A) and in Scheme 7a results in a negative electron affinity. Obviously, partitioning of the molecule by carbon units results in too large a portion of the molecule being represented with a STO-3G basis set. Decreasing the quaternary partition to include only the terminal C_2H_5- group (Scheme 7b) and increasing the size of the secondary and tertiary partitions results in a large improvement in EA but the value is well short of the FB result. Retaining this partitioning scheme and adding a diffuse function to the tertiary basis set increases the electron affinity to 14.1 kcal/mol. The results determined using partitioning Scheme 7b illustrate the need for at least a valence double-zeta basis with diffuse functions to obtain even reasonable EA values.

TABLE 7: Calculated LDBS and Fully Balanced Basis Set Electron Affinities for the Heptatrienyl Radical Using Various Partitions (see Scheme 7) and Tertiary Basis Sets

		electron affinity		
partitioning scheme	tertiary basis set	LDBS	balanced basis	exptl
a	6-31G(d)	−3.0		
b	6-31G(d)	8.1		
b	6-31+G(d)	14.2	28.9	29.3 ± 0.7
c	6-31G(d)	26.6		
c	6-31+G(d)	27.9		

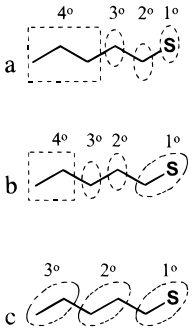
[a] Also shown is the experimental electron affinity from ref 34. All values are in kcal/mol.

TABLE 8: Calculated LDBS and Fully Balanced Basis Set Electron Affinities for the Pentylthio Radical Using Various Partitions (see Scheme 8) and Tertiary Basis Sets

		electron affinity		
partitioning scheme	tertiary basis set	LDBS	balanced basis	exptl
a	6-31G(d)	40.0		
b	6-31G(d)	41.9		
b	6-31+G(d)	42.0	46.1	47.5 ± 0.5
c	6-31G(d)	44.5		
c	6-31+G(d)	44.9		

[a] Also listed is the experimental electron affinity from ref 34. All values are in kcal/mol.

SCHEME 8: Partitioning Schemes Used for the Pentylthio Radical Electron Affinity Calculations[a]



[a] The basis set assignments for each partition are given in the text.

In Scheme 7c, the primary partition is extended to include the three carbon units while the remainder of the molecule is divided into secondary and tertiary sections. This gives a respectable electron affinity of 26.6 kcal/mol, only 2.3 kcal/mol lower than the FB value. Finally, the addition of a diffuse function to the tertiary basis set raises the EA by 1.3 kcal/mol, giving a value that is within 1 kcal/mol of the balanced basis value and 2 kcal/mol of experiment.

The partitioning scheme for the pentylthio radical is as shown in Scheme 8 while calculated electron affinities are listed in Table 8. Balanced basis and experimental[34] values of 46.1 and 47.5 kcal/mol, respectively, are also shown in the Table.

The default partitioning scheme used for pentylthio (see Scheme 8a) appears to reproduce much more closely the balanced basis electron affinity relative to the similar calculations for the heptatrienyl radical (Scheme 7a). The electron affinity in this case is predicted to be too low by only 6.1 kcal/mol. This verifies our intuition regarding the ease with which

nonconjugated systems are treated relative to extended conjugated systems.

Upon increasing the size of the primary partition and decreasing the size of the quaternary region (Scheme 8b), the electron affinity is improved by 2 kcal/mol to 41.9 kcal/mol. Interestingly enough, the addition of diffuse functions to the tertiary basis in this partitioning scheme does little to increase the electron affinity. This implies that electron attachment is more localized in this system relative to the heptatrienyl radical.

Eliminating the quaternary partition altogether and increasing the sizes of the secondary and tertiary partitions increases the electron affinity by another 2.5 kcal/mol. The inclusion of a diffuse function in the tertiary partition basis set raises the EA to 44.9 kcal/mol, 1.2 kcal/mol lower than the balanced basis result. With the FB value being 1.4 kcal/mol lower than experiment, the use of Scheme 8c with a 6-31+G(d) tertiary basis set underestimates the experimental electron affinity by 2.6 kcal/mol.

In summary, balanced basis set electron affinities are much more difficult to reproduce using the LDBS approach than other properties studied here. For both the heptatrienyl and pentylthio radicals, *extensions of the suggested partitioning schemes and the inclusion of a diffuse functions in the bases of all partitions were required to approach the balanced basis set electron affinities*. With these measures, *locally dense basis set electron affinities underestimate the balanced basis results by about 1 kcal/mol.*

The difficulties associated with the application of the LDBS approach to the computation of electron affinities should also be encountered in the treatment of ionization potentials (IP). This is a result of electron loss (attachment) occurring from (to) an orbital that can be completely delocalized over the entire molecule. However, we have recently demonstrated that accurate ionization potentials for relatively large molecules can be obtained using model B3LYP calculations with a small basis set.[35] Consequently, the LDBS determination of IPs is unnecessary.

IV. Summary

It has been shown that the locally dense basis set approach can reproduce balanced basis set bond dissociation enthalpies for the propene molecule using several computational procedures. This finding agrees with the more general results of Chesnut and Byrd[20] who demonstrated the applicability of LDBS with several methods to the determination of total electronic energies.

Absolute and relative O−H bond dissociation enthalpies for a series of *para*-substituted phenols were very well predicted, with values being within about 1 kcal/mol of the balanced basis set values, even with partitioning schemes which boarder on the ridiculous. Recently, Pratt et al. applied the LDBS approach (as outlined in section II) to a series of para-substituted benzylhalide compounds (halides = F, Cl, Br) and found similarly good agreement with balanced basis BDEs.[36] This, combined with our accumulated experience in applying LDBS to the calculation of BDEs, leads us to the conclusion that the procedure is well suited to the determination of this property. In fact, with the appropriate application of the suggested partitioning scheme and basis sets discussed in the section II, we have yet to find a case where the procedure fails.

Good results from the solvation energy calculations for *para*-dimethylamino and *para*-nitrophenol and their radicals were obtained despite the fact that the application of unbalanced basis sets necessarily results in unbalanced electronic density (as measured by the dipole moments). For these molecules solvation energies are predicted to be within 2.5 kcal/mol of the balanced basis results. Furthermore, solvent phase bond dissociation enthalpy differences for these species were found to be within about 1 kcal/mol of the balanced basis set values. This improved agreement was found to be due to error cancellation. These results suggest that LDBS might be useful for this particular application. Given that solvation calculations are inherently difficult from the perspective of wave function convergence and large computer times, an approach that may rapidly and accurately perform these types of computations would be welcome.

Both internal and external hydrogen-bond strengths were very well reproduced using the LDBS approach. Results for this property were found to be in essentially exact agreement with those determined using balanced bases whether the hydrogen-bond donor was treated as primary or tertiary. This implies that the LDBS approach may prove very useful in the quantum mechanical treatment of explicitly solvated systems.

The activation energies for the Diels−Alder reaction of propenal with 2-methyl-1,3-butadiene and 2-*tert*-butyl-1,3-butadiene were found to be in excellent agreement with the fully balanced basis set results. If one considers that the activation energy in this case represents a partial bond breaking and formation process, and realizing that the LDBS approach accurately reproduces balanced BDE results, the findings here are not surprising.

For proton and electron affinities (and implicitly ionization potentials), it appears that the addition of a full charge perturbs molecular systems to such an extent that a direct application of the suggested partitioning and basis sets could not be made. However, some success was observed when partitions were extended and basis sets were augmented with diffuse functions (for EAs). The present results suggest that, for these properties, the locally dense basis set approximation can be applied but should be done so with care.

Finally, it is worthwhile noting the computational efficiency of the LDBS approach. For the determination of the dimethylaminophenol O−H bond dissociation enthalpy (section III.B), the balanced basis evaluation of this property required about four times more CPU time than the LDBS calculation. The relative performance of LDBS versus full basis methods will improve with the number of atoms in the 2°−4° regions.

V. Comparisons and Applications to Other Methods

The locally dense basis set approach is most readily compared to the ONIOM method of Svensson et al.[32] In fact, the ONIOM formulation of determining molecular energies by combining energies determined at different levels of theory strongly resembles the LDBS approach used by Chesnut and Byrd[20] to determine QCISD energies for certain molecular systems.

At first glance, LDBS (as applied presently) and ONIOM appear to be quite similar and, indeed, the philosophies behind the approaches are the same (identifying the centers at which the chemistry is occurring and give them a better description). There is an inherent difference, however, between the two approaches: the application of LDBS generates a single wavefunction for the entire molecular system at the chosen level of treatment whereas ONIOM can, at best, only generate a wavefunction for the whole system at the lowest level of treatment. This important difference has implications for properties like bond dissociation enthalpies: since the entire system is only treated at the lowest level, properties that are dependent

on interactions between the high-level and low-level subsets of the molecule are only as good as the low-level treatment.

Consider the example of 1,2-dihydroxybenzene that was treated using LDBS and the "default" partitioning scheme (see Scheme 4 in section III.D). The calculated BDE using this approach was found to be 77.9 kcal/mol, in exact agreement with the balanced basis treatment. If the same partitioning scheme and basis sets were used in an ONIOM approach, the interaction between the two hydroxy groups is determined at the B3LYP/6-31G(d) level. The resultant BDE for 1,2-dihydroxybenzene using the ONIOM approach with these parameters is predicted to be too low by 0.8 kcal/mol. While this error seems small, the errors associated with the ONIOM procedure may prevent the determination of these types of properties to within the 1 kcal/mol target. These types of problems are typical of capped subsystem type approaches and may be avoided through the use of locally dense basis sets since molecular subsystems are treated as being continuous.

Generally speaking, however, the ONIOM approach has the advantage of being able to treat much larger molecular systems due to the ability to incorporate semiempirical or molecular mechanics methods into the procedure. It should be possible to extend the applicability of both the LDBS approach and the ONIOM procedure by combining the two methodologies. Such a method would allow for the extension of the ONIOM high-level system with a corresponding increase in the accuracy of determined properties without a significant increase in computer resources. Recent work by Truhlar's group[37,38] on a few small molecules illustrates the potential of a combined LDBS/ONIOM approach.

The LDBS approach may also have application in other methods. The divide-and-conquer (DAC) method of Yang[3] is formulated in such a way so that a large molecule is partitioned into smaller fragments. With the inclusion of a certain number of buffer atoms, Yang has shown that the electronic density associated with each fragment can be accurately computed and that the fragment densities can be "assembled" to obtain the electronic density for the whole molecular system. The application of locally dense basis sets to this method is obvious: the number of basis functions can be attenuated as a function of distance from a fragment. As a result, LDBS can be used to increase the number of the buffer atoms in the calculation and thereby improve the accuracy of the divide-and-conquer approach. Alternatively, DAC computational performance can be improved using the default number of buffer atoms by a reduction in the number of basis functions applied to them.

The locally dense basis set approach may even be applied to G2[6] calculations for the determination of bond dissociation enthalpies. For example, the ethanol O−H BDE may be determined using "G2(LDBS)" by constraining the C_2H_5- moiety basis set to 6-31G(d) while allowing the −OH group to be represented using the various bases utilized in a normal G2 calculation. This combination results in BDEs that agree to within 1.1 kcal/mol of both the G2 and G2(MP2) BDEs. Even better agreement was obtained for the C−O BDE in dimethyl ether and the central C−C BDE in butane.

Ultimately, any method utilizing basis functions for the determination of properties such as those studied in this work could be easily modified to include the LDBS approach. Invariably, such a modification will result in improvements in computational efficiency with little loss in accuracy.

VI. Suggested Guidelines for the Application of LDBS

It is clear that, for the computation of certain properties, the performance of the LDBS approach strongly depends on the underlying methodology to which it is applied. If, for example, a BDE or activation energy is poorly predicted using a given method, the locally dense basis set approach when properly applied will at best reproduce the properties predicted by the chosen method. Furthermore, the limiting case of the LDBS approach is simply a balanced basis set calculation. From this perspective it becomes clear that errors do not arise out of the partitioning of a molecule but rather out of the basis set assignments made to the individual partitions. Therefore, care must be taken in making basis set assignments.

The user of the LDBS approach must also keep in mind that the underlying assumption in the approach is that the property of interest is localized. As such, it is important to identify *a priori* the changes, e.g., in geometry, conjugation, etc., that occurs *during or as a result of* the chemical process. This can usually be accomplished through the use of a low-level method such as AM1 or molecular mechanics procedures. Generally speaking, if all such changes are identified and properly described with the appropriate partition/basis, the application of locally dense basis sets should accurately reproduce balanced basis results for the process under investigation.

In the sections discussing the calculation of proton and electron affinities, it was shown that it was necessary to alter partitioning and basis sets in order to obtain reasonably accurate results. This indicates that, under certain circumstances, the LDBS approach can produce poor results and suggests that each problem requires a unique partitioning and/or basis sets assignment. While this assessment may be true in some cases, we have already shown that for selected properties, our suggested approach to partitioning works quite well. However, it is prudent to apply the LDBS approach cautiously to systems with unknown behavior. This is particularly true for systems for which there is no obvious partitioning scheme (e.g., extended conjugated systems). As a careful approach, we suggest beginning with the partitioning scheme given in section II.A and adjusting the partitioning until convergence in the property of interest is reached. We have seen that results tend to follow regular trends and converge fairly rapidly with initial partitioning and basis sets which are well chosen.

For studies involving a series of related compounds, e.g., BDEs in substituted phenols or QSAR studies, we suggest applying partitioning schemes/basis sets which are as consistent as possible for all members of the set. By doing so, additional error cancellation will likely offset any inadequacies in the assignments.

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