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An Evaluation of Various Computational Methods for the Treatment of Organoselenium Compounds

Jason K. Pearson, Fuqiang Ban, and Russell J. Boyd*

Department of Chemistry, Dalhousie University, Halifax, Nova Scotia, Canada B3H 4J3

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A reliable computational method for the prediction of organoselenium geometries and bond dissociation energies (BDEs) has been determined on the basis of the performance of density functional theory (DFT: B3LYP and B3PW91) and ab initio molecular orbital procedures (Hartree−Fock (HF)) in conjunction with various Pople basis sets including (but not limited to) the 6-31G(d), 6-31G(d,p), 6-311G(d), 6-311G(d,p), 6-311G(2df,p), and 6-311G(3df,3pd) sets. Predicted geometries and BDEs are compared with available experimental data and quadratic configuration interaction including single and double substitutions (QCISD) results. The B3PW91/6-311G(2df,p) level of theory is recommended for the prediction of the geometries and energetics of organoselenium compounds.

Introduction

Selenium is an essential element in the human body and is most prevalent in what is commonly known as the 21st natural amino acid, selenocysteine (Sec). This amino acid is a vital component to several antioxidant enzymes in mammals, most notably the glutathione peroxidase (GPx) enzyme,[1−5] which catalyzes the reduction of harmful peroxides by the thiol glutathione (GSH) and protects the lipid membranes and other cellular components against oxidative damage. Oxidative damage has been implicated in a variety of degenerative human conditions including various disease states and even the aging process.[6,7]

There have been attempts to mimic GPx activity with model systems.[8−16] The basic catalytic cycle of GPx is presented in Figure 1.[17−19] The selenoenzyme in its selenol form (Enz-Se-H) is oxidized to the selenenic acid derivative (Enz-SeOH) by reduction of the peroxide to an alcohol. GSH then reacts with Enz-SeOH to form a selenenyl sulfide (Enz-Se-S-G) intermediate and releases a water molecule. A second GSH converts the intermediate to the original selenol and in the process produces the oxidized glutathione (GSSG). Diselenides[8−10,13,14,20−22] and allyl selenides[10] are the most common GPx mimics in the literature, and within this relatively large classification many derivatives are possible.

Despite extensive experimental studies with biologically relevant selenium compounds, it is not fully understood why selenium is such a powerful antioxidant. To obtain greater insight into the properties and reactions of selenium compounds, we plan to carry out high-level quantum chemical computations.

Bachrach and Jiang have noted that an evaluation of computational methods for selenocarbonyl systems[23] and other biologically relevant organoselenium compounds has not been reported, although the redox chemistry of organoselenium compounds has been investigated theoretically[24] as well as a recent study on the selenium-containing antioxidant ebselen.[25] Thus, it is desirable to determine a suitable computational method for the prediction of the properties of selenium compounds. Accordingly, we have performed a systematic theoretical study on a series of eleven organoselenium compounds (see Figure 2) that were chosen as models of biologically relevant selenium compounds.

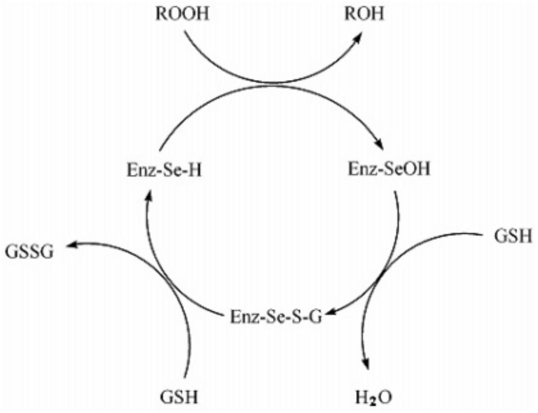

Figure 1. The catalytic cycle of GPx.

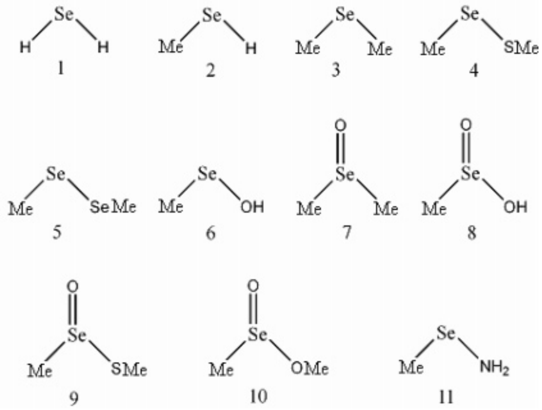

Figure 2. The 10 organoselenium compounds included in this study.

Figure 1 demonstrates the relevance of the selenides (**1** and **2**), selenenic acid (**6**), and selenenyl sulfide (**4**) in the investigation. An additional catalytic process has been proposed for selenium[26] based on the redox chemistry of simple aromatic selenium compounds[27] that involves a seleninic acid (**8**) as well

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* Corresponding author e-mail: russell.boyd@dal.ca.

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as a thiolseleninate ester (**9**), which prompted their inclusion in this study. Selenoxides (**7**) and seleninate esters (**10**) have also been implicated as potential intermediates within catalytic selenium processes.[10] Finally, the many attempts to mimic the activity of the GPx enzyme have led to investigations of diselenides (vide supra) (**5**) and nitrogen-containing selenium compounds[21,28−31] (**11**), and therefore they are also included in this study. [For information on the nomenclature of selenium compounds, the reader is referred to the work by Guenther (Guenther, W. H. In *Organic Selenium Compounds: Their Chemistry and Biology*, Klayman, D. L., Guenther, W. H., Eds; Wiley-Interscience: New York, 1973; pp 1−12.)].

To determine a suitable computational method for selenium compounds, it is first desirable to ascertain the basis set at which the results converge (i.e., no appreciable difference in the calculated properties of the molecule are obtained by including more basis functions). The basis set where the results converge depends on the criteria used to measure it. For example, the length of a particular type of bond may converge sooner than another. It is also contingent upon the threshold within which it is decided that no appreciable change has been obtained. For the current work, the parameters studied were the bond lengths, bond angles, and bond dissociation energies (BDEs) associated with selenium and a threshold of no greater than 0.005 Å for a bond length, 0.5° for a bond angle, and 5 kJ mol^{-1} ($\approx$1.2 kcal mol^{-1}) for a BDE was assumed to be adequate. The converged parameters of the model selenium-containing systems can be compared with available literature values or computational reference values (from QCISD), and the “best method” can be selected based on their relative performances.

Computational Methods

All calculations for this paper were performed with the Gaussian 98[32] or Gaussian 03[33] suite of programs. Geometry optimizations and frequency calculations for thermochemical analysis were performed with various Pople basis sets[34] of increasing complexity at different levels of theory, including Hartree−Fock (HF), density functional theory (DFT), and quadratic configuration interaction (QCISD) methods. HF was chosen as a reasonable ab initio starting point for the work. Hybrid DFT calculations were carried out using Becke’s three-parameter exchange functional[35] (B3) in conjunction with the correlation functional proposed by Lee, Yang, and Parr[36] (LYP) as well as the PW91 functional of Perdew and Wang.[37] These methods were chosen based on their general applicability. Because of our interest in larger biological systems involving selenium, higher-level methods are not considered in this paper, except to establish a theoretical reference where experimental data are not available to evaluate the performance of the selected DFT methods. We have used QCISD for this purpose. For some reference calculations Dunning’s correlation consistent triple-ζ basis set (cc-pVTZ)[38] was used.

Vibrational frequencies were not scaled in the BDE calculations. This choice was made to circumvent the testing of scale factors rather than the methods themselves. Furthermore, it is well-known that optimized scale factors for DFT-based methods are close to unity.[39]

Results and Discussion

TABLE 1: Optimized Carbon−Selenium Bond Lengths (Å) for Dimethyl Selenide

basis set	B3PW91	B3LYP	HF
6-31G(d,p)	1.9488	1.9634	1.9497
6-31+G(d,p)	1.9455	1.9615	1.9451
6-31++G(d,p)	1.9436	1.9599	1.9494
6-311G(d,p)	1.9541	1.9693	1.9526
6-311+G(d,p)	1.9541	1.9695	1.9527
6-311++G(d,p)	1.9542	1.9695	1.9527
6-311G(2df,p)	1.9474	1.9626	1.9467
6-311++G(2df,p)	1.9474	1.9626	1.9465
6-311G(3df,3pd)	1.9470	1.9621	1.9472
6-311++G(3df,3pd)	1.9469	1.9620	1.9473

TABLE 2: Optimized Carbon−Carbon−Selenium Bond Angles (deg) for Dimethyl Selenide

basis set	B3PW91	B3LYP	HF
6-31G(d,p)	97.61	97.48	100.64
6-31+G(d,p)	97.22	97.14	100.45
6-31++G(d,p)	98.30	98.17	100.47
6-311G(d,p)	97.31	97.18	100.36
6-311+G(d,p)	97.30	97.17	100.52
6-311++G(d,p)	97.31	97.18	100.52
6-311G(2df,p)	97.37	97.24	100.92
6-311++G(2df,p)	97.37	97.24	101.03
6-311G(3df,3pd)	97.40	97.27	100.85
6-311++G(3df,3pd)	97.41	97.27	100.93

Our first step was to optimize the structures in Figure 2 with the HF, B3LYP, and B3PW91 methods in conjunction with a series of basis sets. Table 1 shows the optimized carbon−selenium bond lengths for dimethyl selenide (in Å). Over the entire series it can be seen that the addition of diffuse functions causes no appreciable change ($>$0.005 Å) in the bond length. This is understandable because the system under investigation is not anionic and does not involve large diffuse electron clouds. This is true for all systems studied. In the case of the bond angles about selenium, similar results were observed. Table 2 demonstrates again that diffuse functions are not important for organoselenium geometries. The B3LYP and B3PW91 functionals converge to similar geometries; however, it can be seen that diffuse functions do not appreciably change ($>$0.5°) the bond angle. Due to the negligible effect of diffuse functions on the geometry of dimethyl selenide, and on all other molecules studied, diffuse functions have been neglected in the following discussion.

We have assessed the behavior of the HF, B3LYP, and B3PW91 methods for the prediction of geometrical parameters associated with the selenium atom as well as bond dissociation energies of selenium bonds. The results of the HF, B3LYP, and B3PW91 methods with respect to the basis set are similar, and therefore we only report the B3PW91 results in Figure 3.

Figure 3 illustrates the variation of the predicted bond lengths (in Å) with respect to the basis set with the B3PW91 method for the carbon−selenium bond in all molecules under investigation. It can be seen that with triple-ζ basis sets, an increase in the number of basis functions shortens the Se−C bond length as it approaches that of the largest (6-311G(3df,3pd)) basis set. Since the 6-311G(2df,p) basis set results are not significantly different from the 6-311G(3df,3pd) results in any case, we conclude that it produces geometrical parameters with sufficient accuracy so as to not warrant using a larger basis set with a given method. Figure 3 shows that the 6-31G(d,p) geometries are consistently close to the 6-311G(2df,p) results for carbon−selenium bonds suggesting that the 6-31G(d,p) basis set could be used as a reliable starting point.

For the selenium−oxygen bond in our selected molecules, both formal single and double bonds are present. Compounds **7** and **9** possess only a selenium−oxygen double bond,

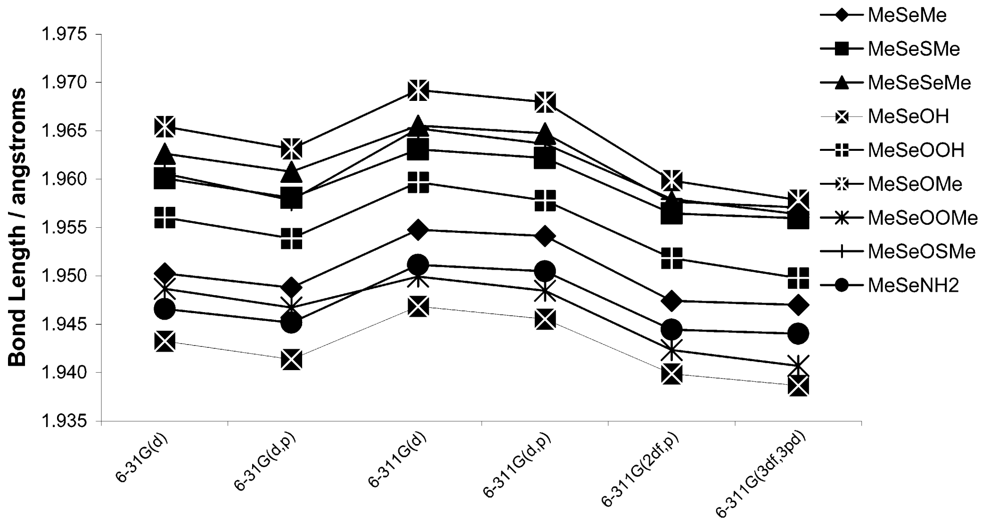

Figure 3. The optimized carbon−selenium bond lengths for all molecules under investigation (having a carbon−selenium bond) with respect to the basis set with the B3PW91 method.

TABLE 3: Optimized Oxygen−Selenium Bond Lengths (Å) for All Molecules Having Such a Parameter Calculated with the B3PW91 Method[a]

basis set	MeSeOH	MeSeOOH	MeSeOOMe	MeSeOSMe	MeSeOMe
6-31G(d)	1.822	1.818 (1.641)	1.836 (1.640)	(1.659)	(1.640)
6-31G(d,p)	1.820	1.816 (1.641)	1.836 (1.640)	(1.659)	(1.640)
6-311G(d)	1.833	1.831 (1.636)	1.850 (1.635)	(1.656)	(1.635)
6-311G(d,p)	1.836	1.834 (1.636)	1.850 (1.635)	(1.657)	(1.635)
6-311G(2df,p)	1.808	1.798 (1.623)	1.813 (1.622)	(1.640)	(1.622)
6-311G(3df,3pd)	1.811	1.801 (1.623)	1.815 (1.622)	(1.641)	(1.622)

[a] Values in parentheses represent oxygen−selenium double bonds.

TABLE 4: Calculated Selenium Bond Lengths for Selected Test Molecules with the 6-311G(2df,p) and 6-311G(3df,3pd) Basis Sets Using the B3PW91 Method

molecule	parameter	6-311G(2df,p)	6-311G(3df,3pd)
11	r(Se−N)	1.861	1.860
4	r(Se−S)	2.185	2.183
9	r(Se−S)	2.287	2.284
5	r(Se−Se)	2.318	2.318

TABLE 5: Maximum Deviation of Carbon−Selenium−X Bond Angles (deg) for All Molecules Having Such a Parameter over the Entire Series of Basis Sets Used with the B3PW91 Method

molecule	maximum deviation
H_2Se	0.65
MeSeH	0.91
MeSeMe	1.27
MeSeSMe	0.73
MeSeSeMe	1.16
MeSeOH	1.17
MeSeOOH	0.51
MeSeOMe	1.09
MeSeOOMe	0.90
MeSeOSMe	1.19
$MeSeNH_2$	1.39

compound **6** contains only a selenium−oxygen single bond, and compounds **8** and **10** contain both a selenium−oxygen single bond and a selenium−oxygen double bond. Table 3 shows that the 6-311G(2df,p) basis set essentially reproduces the results of the larger 6-311G(3df,3pd) basis just as in the case of the selenium−carbon bond. The same behavior is also observed for the case of the selenium−nitrogen, selenium−sulfur, and selenium−selenium bonds, which is demonstrated in Table 4.

Table 5 shows the maximum deviation (defined as the difference between the maximum and minimum values) of the carbon−selenium−X bond angle (in degrees) calculated for those molecules that have such an angle. From the table it is clear that there is little fluctuation in the angle with respect to basis set.

The accuracy of the optimized geometries of selenium containing compounds can be assessed by the comparison with experimental values or the QCISD results. There are generally three issues that arise when calculated parameters are compared with experimental data. The first is whether the desired experiment has been performed and therefore the availability of experimental data. Often (and indeed in this study) there are many experimental parameters that are simply not available.

The second issue is exactly the opposite of the first. There are instances where multiple reports of the same molecular property are found in the literature, and when these reports conflict it may not be a trivial task to discern the most accurate value. The authors have found 26 reported carbon−selenium bond lengths for noncyclic systems with saturated carbon atoms in the literature. These range from 1.8 Å[40] to 2.08 Å,[41] which encompasses the entire breadth of our calculated values (see Figure 3). Narrowing the search to just dimethyl selenide produces an experimental range from 1.925 Å[49] to 1.977 Å,[46] which again places all of our calculated values within the experimental range (see Figure 3). A careful comparison is required because in many cases the agreement between theoretical and experimental values depends on the choice of experimental value.

Finally, there also exist instances where the error associated with a particular experimentally determined value is so large that all calculated values fall within its uncertainty. This circumstance dictates that no conclusions can be drawn as to which computational method comes closest to the "real" value.

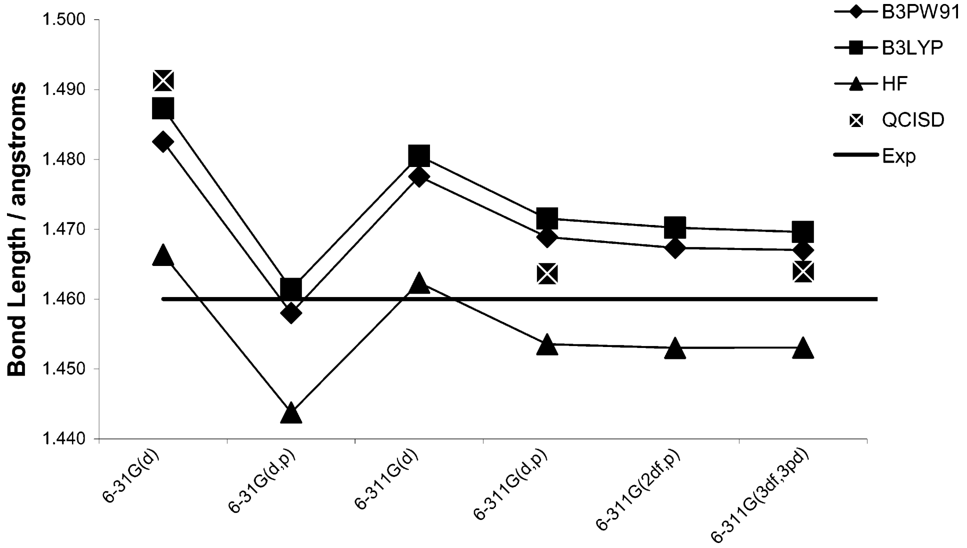

Figure 4. The optimized selenium−hydrogen bond lengths of H_2Se at various levels of theory with respect to the basis set (three QCISD values are shown). Included in the figure is the experimental bond length.

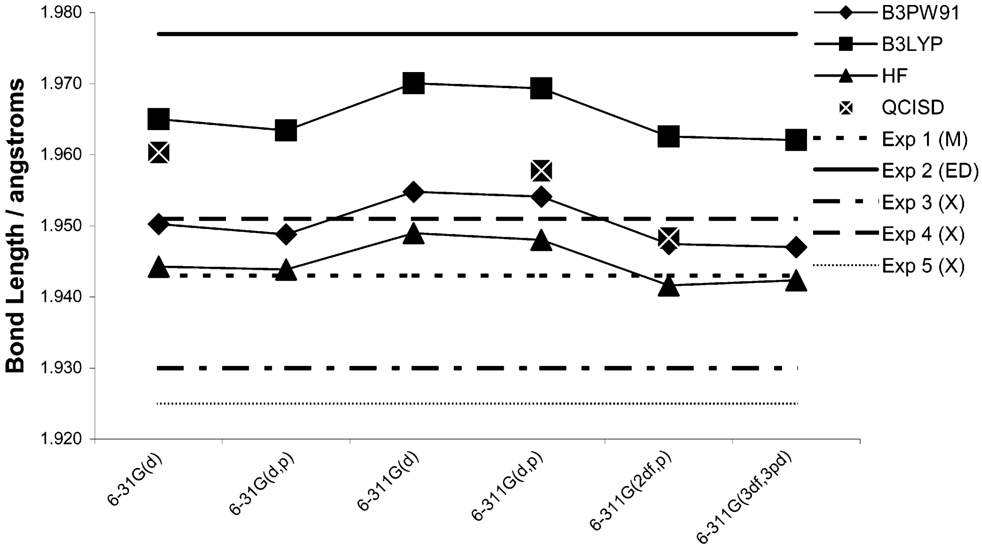

Figure 5. The optimized carbon−selenium bond lengths of dimethyl selenide at various levels of theory with respect to the basis set (three QCISD values are shown). Also shown are the available experimental bond lengths. M corresponds to a microwave experiment, ED corresponds to an electron diffraction experiment, and X corresponds to an X-ray experiment.

For these reasons, the reported values need to be scrutinized, and one must make an effort to choose appropriate examples from the literature for comparison. Three reports on the experimental geometry of H_2Se (**1**) were found, and all agree very well with each other and to a good degree of precision.[42−44] This eliminates the above-mentioned problems with experimental comparison and is therefore a good starting point to determine the most suitable level of theory for predicting equilibrium geometries. Figure 4 illustrates the calculated selenium−hydrogen bond length (in Å) for the selected levels of theory with respect to the basis set. Also included in Figure 4 is the experimental value from three separate sources,[42−44] all of which are exactly equal. With the exception of the high level reference QCISD, the B3PW91 functional yields the value closest to experiment at a point where the geometry has converged. This result also lends support to the accuracy of the QCISD method as a reference.

Dimethyl selenide (**3**) is an example of a case where a wide range of experimental data is available, and so a determination of the "best" level of theory is difficult. Figure 5 illustrates the calculated bond lengths (in Å) of dimethyl selenide as well as the available experimental data (exp 1−5 correspond to the values from refs 45 through 49, respectively). Depending upon which experiment one chooses to compare the calculations to, a different conclusion can be drawn. This is a case where the QCISD results with sufficiently large basis sets can be used as a theoretical reference to check the quality of results obtained from much less expensive DFT methods. It can be seen that the geometry of the B3PW91/6-311(2df,p) procedure and beyond agrees very well with the QCISD results.

Figure 6 illustrates the hydrogen−selenium−hydrogen bond angles (in degrees) for various levels of theory with respect to the basis set. Although the three available experimental values differ slightly,[42−44] the B3PW91 functional still performs exceptionally well at and beyond the 6-311(2df,p) basis set. It is also close to the QCISD reference as it is in many other cases and so remains the best choice for organoselenium geometries.

To concisely illustrate the performance of each method for geometrical parameter prediction on all test molecules with respect to the basis set we show the root-mean-square deviation of all selenium bond lengths relative to a QCISD/cc-pVTZ reference optimization in Figure 7. The cc-pVTZ basis set was

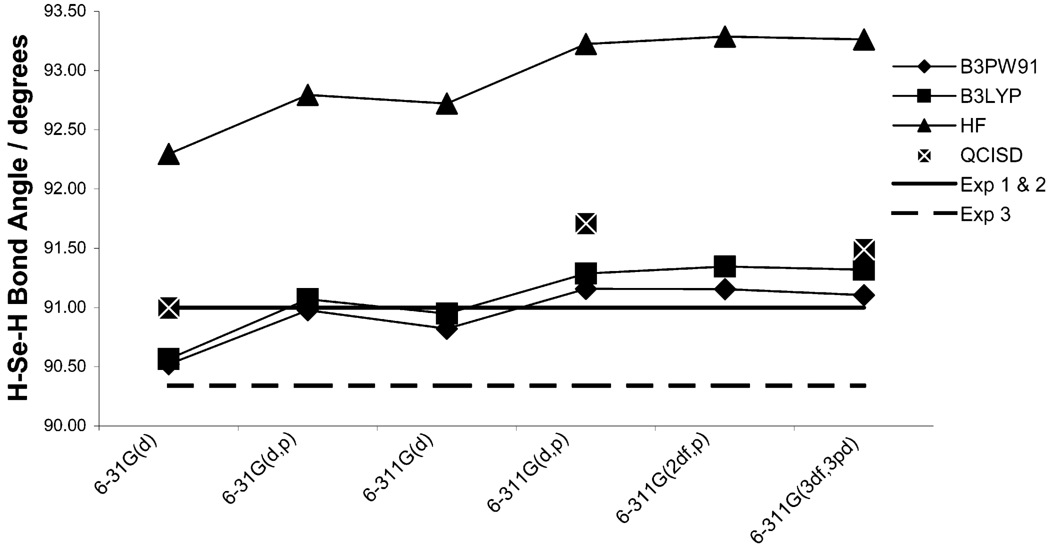

Figure 6. The optimized hydrogen−selenium−hydrogen bond angles of H_2Se (in degrees) at various levels of theory with respect to the basis set (three QCISD values are shown). Included in the figure are the available experimental bond angles.

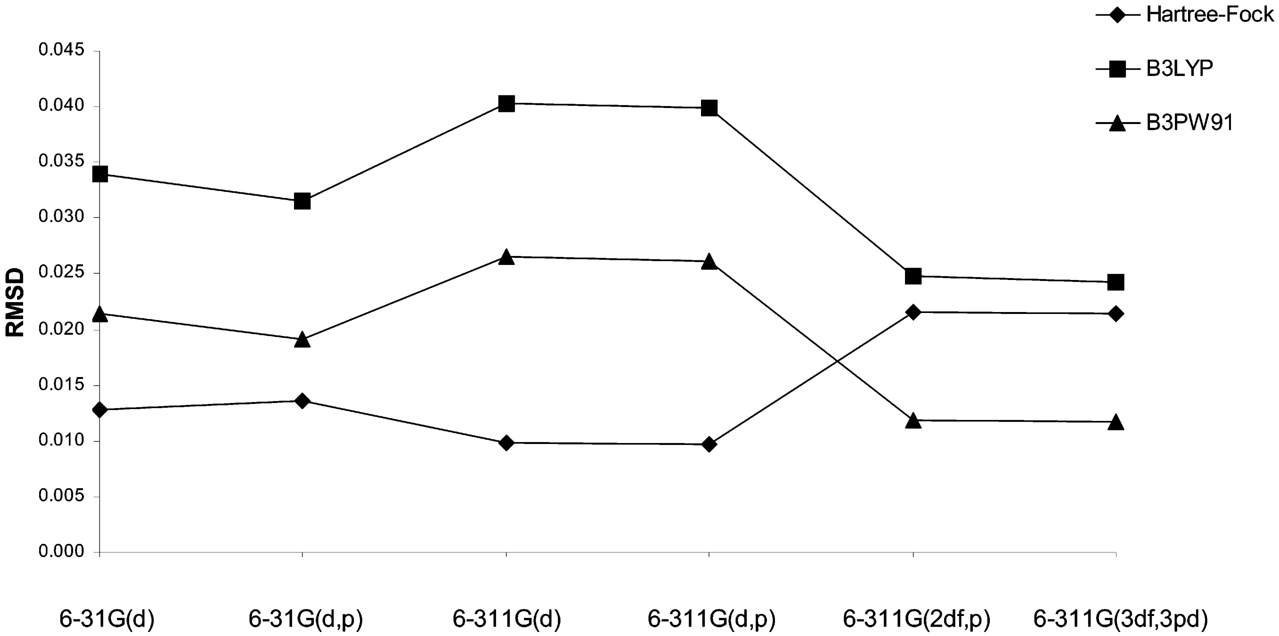

Figure 7. RMSD performance of each method at predicting bond lengths associated with selenium. Here RMSD = $\sqrt{\Sigma(x-x_{\mathrm{ref}})^2/n}$, where x_{ref} refers to the QCISD/cc-pVTZ value of the given parameter.

chosen as a reliable high-level reference that was also different from any basis set used in Figure 7 so that the RSMD of any particular point would not be artificially lowered due to a cancellation of errors. As can be seen in the figure, accurate geometrical parameters are obtained with the B3PW91 functional at high basis sets. It should be noted, however, that the HF method consistently produces reliable results with the 6-311G(d) and 6-311G(d,p) basis sets, which can be attributed to a cancellation of errors.

For every compound studied and for every basis set, HF predicts the smallest bond lengths, while B3LYP predicts the longest, with B3PW91 falling in the middle and closest to experimental values and/or QCISD reference values. Thus, confidence in the B3PW91 functional for organoselenium geometries is strengthened.

To test the accuracy of the selected methods in terms of the energetics of organoselenium compounds, BDEs were considered. The BDE of all single bonds to the selenium atom were calculated by subtracting the energy of the full molecule from the sum of the energies of the radicals generated by homolytic cleavage.

$$\mathrm{BDE(A\text{-}B) = E(A\cdot) + E(\cdot B) - E(A\text{-}B)}$$

The energy of each species included the zero-point and thermal corrections to 298.15 K generated from a vibrational frequency calculation. As with the geometrical parameters, the energies of the test compounds do not significantly change with the addition of diffuse functions. Also, Muang et al.[50] have computed BDEs for a smaller series of organoselenium compounds and have shown that diffuse functions do not significantly affect the BDE computations. For these reasons, they are omitted from the remainder of the discussion. It should be noted that Binning and Curtiss[51] have also reported BDEs of H_2Se in a study of Ge, As, and Se.

It can be seen in Table 6 that for the entire set of test molecules over the series of triple-ζ basis sets used, the

TABLE 6: Calculated BDEs (kJ mol^{-1}) for All Selenium Single Bonds with Respect to the Basis Set for the B3PW91 Method Including the Mean Deviation of Each

		basis set				
molecule	parameter	6-311G(d)	6-311G(d,p)	6-311G(2df,p)	6-311G(3df,3pd)	mean deviation
1	D_o(Se−H)	322.39	330.17	331.58	332.48	3.38
2	D_o(Se-Me)	264.70	262.64	265.61	266.01	1.07
2	D_o(Se−H)	307.48	315.79	316.59	317.47	3.43
3	D_o(Se-Me)	255.68	253.89	256.89	257.25	1.14
4	D_o(Se−S)	216.20	215.89	227.92	228.03	5.96
4	D_o(Se-Me)	212.69	211.32	209.64	210.04	1.08
5	D_o(Se−Se)	212.12	211.80	215.73	216.45	2.07
5	D_o(Se-Me)	206.90	205.38	207.68	207.96	0.84
6	D_o(Se−O)	251.22	250.31	270.11	269.33	9.48
6	D_o(Se-Me)	240.85	240.34	241.58	243.39	0.94
7	D_o(Se-Me)	169.45	168.14	174.33	177.71	3.61
8	D_o(Se−O)	226.33	224.93	249.15	247.35	11.31
8	D_o(Se-Me)	185.19	184.58	187.38	190.13	1.93
9	D_o(Se−S)	142.24	142.69	150.75	151.57	4.35
9	D_o(Se-Me)	174.31	173.32	175.38	177.50	1.31
10	D_o(Se−O)	166.07	165.57	185.43	185.44	9.81
10	D_o(Se-Me)	179.49	178.87	181.79	185.19	2.15
11	D_o(Se−N)	235.27	233.00	241.35	240.75	3.46
11	D_o(Se-Me)	215.41	214.70	217.38	218.75	1.51

calculated BDEs have an average mean deviation of only 4.3 kJ mol^{-1}. This confirms that the BDE values do not change significantly with the addition of more basis functions at the triple-ζ level. Shown in Figure 8 is the predicted BDE of the Se−H bond in H_2Se with respect to the basis set for the various methods. It is well-known that HF underestimates the BDE for homolytic cleavage; however, we include it in our results for completeness. The experimental value[52] of 330 kJ mol^{-1} is also included in the figure. The B3LYP and B3PW91 functionals produce very similar results with the B3PW91 performing slightly better. Due to the scale of the figure, the two essentially overlap. It can be seen that the B3PW91/6-311G(2df,p) method, which was selected as the "best" method for geometries also reproduces excellent BDEs in this case.

We have not been able to find any experimental BDEs for the larger test molecules. It was neither feasible nor necessary however to carry out high-level reference calculations at the QCISD level for all test molecules due to the relatively low variance in the BDE with respect to basis set. Also, Figure 8 demonstrates the accuracy of the B3PW91 method for H_2Se. While it is not fair to say that this functional will reproduce accurate BDEs for larger molecules, it does represent the best choice for such calculations based on our results.

Conclusions

A computational study of eleven organoselenium compounds was performed using the HF, B3LYP, and B3PW91 methods in conjunction with a series of Pople basis sets including (but not limited to) the 6-31G(d), 6-31G(d,p), 6-311G(d), 6-311G(d,p), 6-311G(2df,p), and 6-311G(3df,3pd) sets. For geometrical parameters and BDEs, results were generated that were satisfactory according to what our goals were (vide supra), and the method that performed best was found to be quite accurate and reliable. Therefore, further testing, including other functionals and/or basis sets is not necessary. Reliable geometrical parameters associated with the selenium atom are produced with all methods applied in this study at a reasonably large basis set; however, it was observed that the B3PW91 method and the 6-311G(2df,p) basis set performed slightly better. It was found that HF predicts the smallest bond lengths, while B3LYP

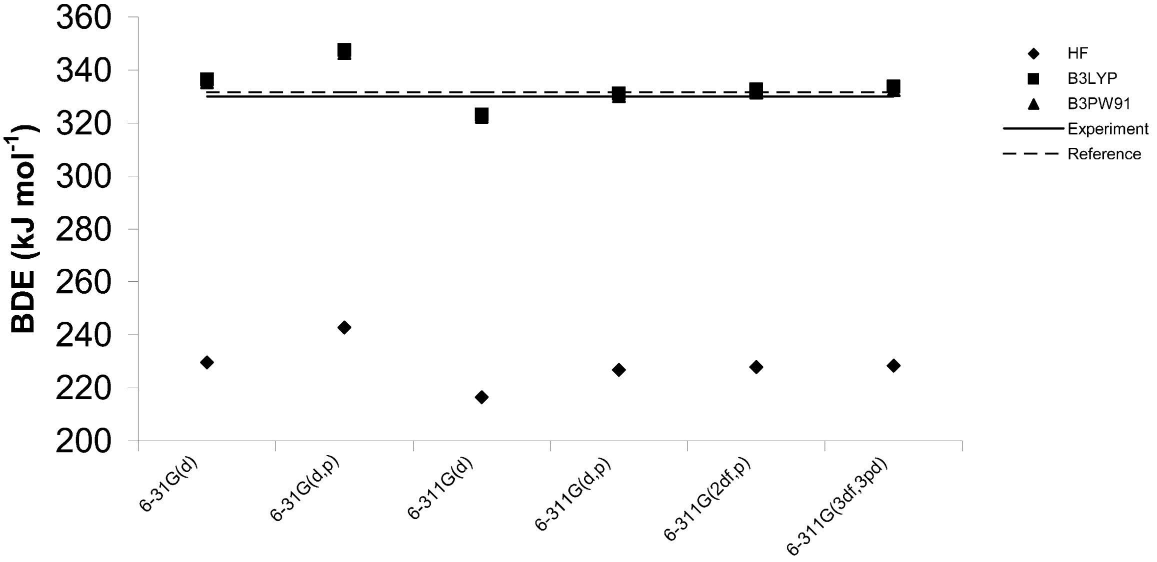

Figure 8. Predicted Se−H BDE for H_2Se using selected computational methods with respect to the basis set with the QCISD/cc-pVTZ value for reference.

predicts the longest, with B3PW91 falling in the middle and closest to the experimental values and/or QCISD reference values.

Similar behavior has been observed with respect to BDEs of organoselenium molecules. Both DFT functionals with a reasonably large basis set produce good results, and the B3PW91 method produces the best agreement with experiment and/or high-level reference values.

We recommend the B3PW91/6-311G(2df,p) level of theory for the reliable prediction of the geometries and energetics of organoselenium compounds.

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Supporting Information Available: Archive entries for calculations involved in Figures 7 and 8 (Tables S1 and S2, respectively). This material is available free of charge via the Internet at http://pubs.acs.org.

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