Localized orbital corrections for the calculation of barrier heights in density functional theory

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Abstract

This work describes the extension of a previously reported empirical localized orbital correction model for density functional theory (DFT-LOC) for atomization energies, ionization potentials, electron affinities, and reaction enthalpies to the correction of barrier heights for chemical reactions of various types including cycloadditions, cycloreversions, dipolar cycloadditions, S_N2's, carbon radical reactions, hydrogen radical reactions, sigmatropic shifts, and electrocyclizations. The B3LYP localized orbital correction version of the model (B3LYP-LOC) reduces the number of outliers and overall mean unsigned error (MUE) vs. experiment or *ab initio* values from 3.2 to 1.3 kcal/mole for barrier heights and from 5.1 to 1.1 kcal/mole for reaction enthalpies versus B3LYP. Furthermore, the new model has essentially zero additional computational cost beyond standard DFT calculations. Although the model is heuristic and is based on multiple linear regression to experimental or *ab initio* data, each of the parameters is justified on chemical grounds and provides insight into the fundamental limitations of DFT, most importantly the failure of current DFT methods to accurately account for nondynamical electron correlation.

I. Introduction

In a series of previous publications, we have developed an approach to improving density functional theory (DFT) methods[1] based on empirical localized orbital corrections (DFT-LOC).[2] When used in conjunction with the B3LYP functional[3] (B3LYP-LOC, which will be the focus of the present publication), these corrections provide a remarkable improvement in atomization energies,[2a] ionization potentials and electron affinities,[2b] and heats of reaction for molecules composed of atoms in the first two rows of the periodic table[2c] as detailed in sections II.A, II.B, and II.D, respectively. Recently we have also demonstrated improvements for thermochemistry of small transition metal species as summarized in section II.C.[2d]

Our aforementioned correction scheme is based upon assignment of parameters using the *equilibrium* geometries (i.e. reactant and product) only. A general theory must enable calculation of the energy of the molecule as a function of the atomic coordinates for an *arbitrary* arrangement of the atoms. This in turn requires that the corrections be formulated as a continuous function, rather than discrete parameters.

Such a function can be easily constructed and optimized, utilizing a molecular mechanics-like formulation, with the addition of empirical terms to rectify errors endemic to B3LYP. These parameters can eventually even be deployed to treat dispersion, an area in which B3LYP is known to perform poorly. Still, optimization of such a function cannot proceed without an

understanding of how the parameters change as bonds are made and broken. We have developed parameters for errors manifested in reactants and products, allowing more accurate calculation of enthalpies, in previous publications and summarized in section II.D. (Note that we do not attempt to correct for errors found in energies of dissociated atoms themselves, but instead correct for the errors found in *differences* of energies exclusively. For example, we studied reaction enthalpies,2d where we considered the differences in energies of the well-defined reactants and products only. By considering these well-behaved species instead of attempting to tackle dissociated atoms, we focus our efforts on areas where DFT has already been shown to produce reasonable results, and therefore can produce remarkable results upon application of corrections schemes such as those we continue to develop.2a−2d) In the intermediate region connecting reactant to product, parameterization of the model is necessary, particularly at the transition state where unusual geometries and effective hybridization states of central atoms are routinely observed. With transition state correction parameters in place, the remainder of the potential surface can be approximated via interpolation between the key stationary points (equilibrium geometry, transition state, and separated reactants and products). Ideally the interpolating function would be modeled after accurate *ab initio* quantum chemical behavior in the bond breaking region. In practice, unrestricted DFT actually performs reasonably well (although not perfectly) in this regime, and highly precise results for the bond breaking region are not critical for the vast majority of practical chemical applications. Consequently, we focus in this paper on the task of developing accurate and robust parameters for B3LYP-LOC for correcting the barrier height at the transition state, fitting to experimental and high quality *ab initio* data for more than 100 chemical reactions taken from the literature.

We have assembled a wide range of reactions4 of various types, encompassing radical reactions, various substitution reactions, additions, cyclizations, and reactions containing neutral, cationic, and anionic species. The size and diversity of the training set is thus larger and more varied than has been used in previous tests of DFT functionals, or in efforts to optimize these functionals.5 In our view, the use of large and diverse data sets is critical to avoid over-fitting, overcome noise in the data set (inevitable as one moves away from the highly filtered experimental data sets employed by e.g. Pople and coworkers in testing and optimizing G3 theory8), and to present to the model a variety of qualitatively different transition state motifs which may require new parameters. The present data set, while still far from completely extensive, does represent progress as compared to alternatives in the literature.5

In many cases, data is available for both forward and backwards reactions, with the barriers related (as mandated by detailed balance) by the enthalpy of reaction. This implies that one cannot obtain good results for both directions, regardless of the parameterization of the transition state model, unless the enthalpies of reaction are accurate. As a result, we have carefully examined the enthalpies of reaction for all of our test cases, with regard to both performance of B3LYP–LOC, and in terms of possible errors in the literature estimates (experimental or derived from high level *ab initio* calculations) of these values. For example, Truhlar and coworkers have assembled a series of radical reactions, which have formed a key component of their DFT test and training sets for many years.7 They incorporate many sophisticated terms into their estimations of experimental barrier heights (e.g. tunneling corrections) which undoubtedly have improved the precision of the data set. Nevertheless, there are cases (noted in the text) where the "experimental" enthalpies of reaction they use are in significant conflict with for example results obtained by the Pople group for the same quantity (as derived from the Pople results for atomization energies,6 which can be combined to yield enthalpies of reaction). In these cases we have had to make decisions concerning which data to employ, and choices are described below. The main point is that the construction of true benchmark data sets for testing barrier height calculations, with well defined error bars, is still a work in progress, and this impinges upon what one can expect in any set of theory/experiment comparisons in these areas. In contrast, for small molecule atomization energies, the ability to

converge high level CCSD(T) calculations with basis set extrapolations, relativistic corrections, etc., provides a means to resolve most disputes concerning interpretation of experimental data around equilibrium geometries. True benchmarks have been available for some time, at least for small molecules as predominantly populate the G2 data set8. For transition states and for geometries far from equilibrium, more sophisticated approaches than CCSD(T) might be required, such as methods based on multireference wavefunctions.

In addition to facilitating the development of new transition state parameters, the present set of reactions provides an opportunity to test the B3LYP-LOC performance for enthalpies of reaction on a new data set, which has not been included in the training set. A subset of the reactions we study here can be constructed from the Pople G3 data base,[6] which we did use as a training set for B3LYP-LOC. Yet, if these reactions are removed, there remain a substantial number of cases to which B3LYP-LOC has never been exposed. The results, reported below, obtained with no parameter adjustment for the equilibrium geometry parameter set, demonstrate that the performance for this test set (which contains some rather complex and unusual molecules) is comparable to that for the training set, further validating the B3LYP-LOC parameterization as robust and applicable outside the domain of its training set with no falloff in the quality of the results. The overall average error for enthalpies of reaction, 1.2 kcal/mole, is comparable to that expected for high level *ab initio* methods such as G3 theory, and is likely within the error bars of the experimental and high level computational data.

The transition state parameterization itself requires a total of 8 new parameters unique to transition states; hence a total of 36 parameters, including 22 for neutral equilibrium species[2a] and an additional 6 for the charged species2b, were utilized in this work. While this number might seem large, it is comparable to the number of parameters exploited by modern DFT functionals such as M06-2X.17 Some of these parameters address new hybridization states that are created by attacks on various types of central atoms and these parameters are generally consistent with those already optimized for enthalpies of reaction.2a Similarly there are a few new parameters for stretched bonds or half bonds, which again are consistent with the equilibrium results[2a] (despite the lack of constraints used in the parameter optimization). Overall, the ratio of the number of new adjustable parameters (8) to that of training set cases (105) appears reasonable, and the parameters can all be physically rationalized in light of previous results.

Charged molecules present a special challenge for the B3LYP-LOC method in that corrections for charging and discharging must be performed via a separate set of parameters, developed in ref. [2b]. We have used the parameters from that reference without adjustment, achieving reasonable results for both anions and cations. Specialized parameters for unusual groups, such as azides, would in fact improve the results, but we have avoided this because we do not believe there is sufficient or diverse enough data to avoid the danger of over-fitting for such cases. Nevertheless, such a path could readily be pursued in the future if additional data were to be generated (e.g. via converged CCSD(T) calculations).

The paper is organized as follows. In section II, we provide a brief summary of the B3LYP-LOC approach, referring to previous papers for detailed discussion of parameterization and validation. Section III presents the development of the B3LYP-LOC model for transition states, introducing the 8 new parameters required for these calculations. Section IV describes the results obtained for the 105 reactions in the training set, for both reaction enthalpies and barrier heights, and discusses the distribution of errors, including possible explanations for the small number of outliers that are observed. Finally, in Section V, the conclusion, we summarize our results and briefly discuss future directions.

II. Overview of the B3LYP-LOC methodology

In this section, we simply review the work on the B3LYP-LOC methodology that has already been published, as this forms the foundation for the work presented herein. Note that no additions or modifications are made to any of the methods presented in our previous publications.

II.A. Atomization energies

The original B3LYP-LOC work[2a] utilized 22 empirically determined, but chemically justified, parameters to reduce the mean absolute deviation for atomization energies on the G3 dataset of 222 molecules from 4.8, for uncorrected B3LYP, to 0.8 kcal/mole for B3LYP-LOC. This value is comparable to that obtained using G3 theory, 1.1 kcal/mole; but, G3 theory incorporates coupled cluster methods, thus making it intractable for larger molecules. Almost all outliers were eliminated with essentially zero additional computational cost beyond standard DFT calculations, as the corrections are applied *a posteriori* in an additive fashion. All corrections are based upon valence bond assignments and are divisible into four major categories: corrections to atoms, corrections to individual bonds, corrections for neighboring bonds of a given bond, and radical environmental corrections. These parameters also provide valuable insight into the fundamental limitations of DFT, specifically, the difficulties exhibited by DFT methods in accurately modeling variations in nondynamical electron correlation across different types of chemical bonds, lone pairs, hybridization states, and singly versus doubly occupied orbitals. [9,10]

To better understand these limitations, first consider the simple case of diatomic hydrogen, H_2. As this molecule is stretched to increasing bond lengths, the exact [Hartree-Fock (HF)] exchange hole remains delocalized over both atoms, even though the true exchange correlation hole is localized over mostly just one atomic center. Combining this exact Hartree-Fock exchange with localized correlation produces a delocalized exchange-correlation hole, which is qualitatively incorrect in nature, producing large errors in DFT calculations that employ a full exact exchange model. This is substantially improved by combining exact exchange with Becke exchange and the generalized gradient approximation, producing a more localized exchange hole. The qualitatively correct behavior of the exchange-correlation hole enabled significant progress to be made in reducing errors for gradient-corrected DFT functionals, such as BP86[12], BLYP13, and PBE14.

Dynamical electron correlation (taken on the length scale of an atom) is well modeled by gradient corrections in the exchange and correlation components of modern functionals; on the other hand, nondynamical electron correlation (taken on the length scale of a bond) is more problematic.[10] Within each localized electron pair (in a bond or lone pair), there is a self-interaction "error" given by the difference in the self Coulomb and exchange terms. Although this self-interaction is necessarily zero for unpaired electrons, i.e. the Coulomb and exchange terms cancel, DFT assigns a non-zero value in this case, resulting in detrimental errors, especially at increasing bond lengths, where the self-interaction becomes very large and negative. In the case of doubly occupied orbitals, we posit that the self-interaction error embodied in DFT is actually used to quantitatively model the nondynamical electron correlation present within a localized bond.9 The addition of a component of Hartree-Fock exchange, as is done in B3LYP and other hybrid functionals, can then be thought of as adjusting the size of the self-interaction term in the DFT exchange functional; since the HF exchange term has no self-interaction, increasing the fraction of HF exchange lowers the remaining self-interaction in the functional. Fitting the fraction of HF exchange to experimental atomization energies then allows a more accurate matching between the self-interaction energy for an electron pair, and what is required to represent non-dynamical correlation for that pair. The success of B3LYP in reducing the average error in atomization energies for the G2 data set, as

compared to the great majority of gradient corrected functionals, is evidence that this approach is successful in realizing its objective.6

However, the addition of HF exchange is effective at treating only the "average" nondynamical correlation in an electron pair in a localized bond, whereas differences in the local environment of various bonds and their effects on the nondynamical correlation are not modeled easily by a localized gradient expansion.[10] Notably, while so-called global hybrid functionals such as B3LYP employ constant fractional admixtures of exact exchange, local hybrid functionals[22] employ position-dependent exact-exchange admixtures, allowing for deviations in the nondynamical correlation to be better modeled at least in principle. This presents a unique and interesting way to address the issue of capturing nondynamical correlation that differs from our own approach, but is not explored further here. Instead, the DFT-LOC methodology rests upon the assumption that the localized nuclear framework supporting an electron pair is a principal factor controlling the deviations in value of the nondynamical correlation from the "average" value within global hybrid functionals. Therefore, empirical corrections are applied based upon these localized frameworks. Consider, for example, the corrections applied to single bonds between heavy atoms of various lengths[(i)]: short (−1.36 kcal/mole), medium (−1.90 kcal/mole) and long (−2.57 kcal/mole). These values become appreciably more negative with increasing bond length. This reflects the notion that as bond length increases, nondynamical correlation becomes more negative (as the electrons have more room to avoid each other) and DFT systematically underestimates this effect with increasing severity. In the extreme case, where there is a charge transfer leading to predominantly ionic bonding (e.g. in NaCl), implying substantial localization of the electron pair of the bond near one atom, the B3LYP results are most severely underbound (by 4.5 kcal/mole for NaCl); this parameter is consistent with the others listed above, and when used to correct all bonds of this type, leads to enormous improvement in B3LYP-LOC predictions for molecules in the G3 data set containing one or more bonds with substantial charge transfer character.

A further problem that can be observed with B3LYP calculations, and other functionals, is that the average error (as judged by the MUE) increases systematically with the size of the molecule under investigation.[15a] For example, the MUE for B3LYP atomization energies for the G2[8], extended G2[8], and G3 datasets are 2.43, 3.08, and 4.81 kcal/mole, respectively, consistent with the increasing average molecular weight of the components of each of these three data sets. This systematic increase in error with molecule size is effectively addressed by the empirical corrections in the LOC scheme. Indeed, *the errors in B3LYP are not random*, but are attributable to the specific localized chemical bonds in each molecule, as well as the local environments of those bonds. It is important to emphasize that other functionals we tested (BLYP, B3PW91, SVWN, BP86, BPW91, B3P86, and later M05-2X and M06-2X) display greater average errors than B3LYP-LOC upon application of LOC corrections, and thus apparently have errors that are less systematic in the LOC framework than B3LYP. Notably, the LOC-corrected versions of these other methods, including other hybrid functionals, GGAs and even the LDA, displayed non-trivial improvements when coupled with LOCs, but are still not comparable to the remarkable improvement displayed by B3LYP-LOC itself. For example the average error in BLYP for the G3 set is reduced from 7.3 kcal/mole to 2.1 kcal/mole, not as good an end point as for B3LYP whose errors were reduced from 3.1 kcal/mole to 0.6 kcal/mole, but still an impressive improvement nonetheless. Effectively, the LOC scheme removes the systematic errors for each bond type, thereby qualitatively diminishing the accumulation of such errors with increasing molecular size to the point where the errors for the G3 data set, which contains much larger molecules, is only a few tenths of a kcal/mole larger than that for the G2 or extended G2 sets. Furthermore, problems with properly modeling cyclic, branched,

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[(i)]For the 6–311++G(3*df*,3*pd*) basis, for example

and linear molecules (for which B3LYP exhibits quite different error patterns) are ameliorated via a simple correction based on nearest neighbors of a given bond, noting that underbinding is present when the atoms comprising the bond make additional bonds that would enable an electron from the initial bond (e.g., long single bonds) to make excursions.

The validity of this method is verified by the successful application of the LOC parameters to the G3 dataset, in which the mean absolute deviation is reduced from 4.8 to 0.8 kcal/mole, a value not only competitive with that of G3 theory, but also demanding orders of magnitude less computational cost. Further, after the application of the LOC scheme the number of B3LYP outliers is substantially reduced. Thus, this DFT-based method consistently achieves near-chemical accuracy. Detailed parameters and results for atomization energies and enthalpies of reaction can be found in refs. 2a and 2c and the accompanying supplementary material.

II.B. Ionization potentials and electron affinities

In a subsequent publication[2b], the B3LYP-LOC methodology was extended from atomization energies to ionization potentials (IP) and electron affinities (EA). In this manner, B3LYP-LOC can now be extended to ionic in addition to neutral molecules with 37 parameters developed specifically for charged species. (Be that as it may, only six of these parameters were employed here, as they cover the most common chemistries, such as those studied in this work.) Further, systems with multiple unpaired spins are also addressed. These new features are requisite for an approach that is aimed at applicability across a wide range of chemical phenomena. The methodology is applied to the G2 dataset of 134 molecules (ionization potentials and electron affinities) with a resultant decrease in MUE (vs. experiment) of 0.137 to 0.039 eV. This error is more than three times smaller than the original B3LYP error and is comparable to the errors obtained with G2 theory, a high level *ab initio* method. Further, the number of outliers is also substantially reduced to levels below that achieved with G2 wave-function-based theory.

As with the B3LYP-LOC application to atomization energies, the corrections are applied *a posteriori* in an additive fashion and therefore account for only a trivial increase in computational cost over uncorrected B3LYP. The 22 empirical parameters from the original work[2a] are employed in addition to parameters exclusive to ions developed in this specific work. Again, these parameters are physically justifiable and provide insight into the fundamental nature of DFT. Unsurprisingly, DFT's failure to accurately model nondynamical electron correlation and self-interaction error contributes substantially to errors in ionization potentials and electron affinities, just as with atomization energies.

Here, the neutral atoms are taken as the reference state and corrections are applied to the atomic or molecular ions and the neutral molecules as necessary. The B3LYP-LOC energy of a charged atom is then given by the sum of the corrections for that charged atom (as specified in reference 2a) and the B3LYP energy for the charged atom. The B3LYP-LOC energy of a charged molecule is given by the full suite of LOC molecular corrections as specified in the original LOC work2a in addition to those corrections defined for the charged species2b.

The original B3LYP-LOC work noted the striking similarity in the atomization energy errors as a function of valence bond structures, using this as the basis for the development of the LOC methodology. An investigation of the errors in electron affinity and ionization potential evidences another set of striking patterns, enabling a facile extension of the previous LOC methodology to these charged species.

For a complete discussion of all the parameters available for ionization potential and electron affinity calculations, the reader is referred to the relevant work[2b] while those IP and EA parameters employed in this work are discussed below. These include corrections for delocalization of positive charge and for the removal or addition of an electron from an atomic

or molecular orbital. The specific implementation of these parameters is discussed in sections II.D.2 and II.D.3 for enthalpies of ionic reactions and in sections III.B and III.C for barrier heights of ionic reactions. For cationic reactions, corrections for delocalization of positive charge included IP_D_A_A-H and IP_D_A_A-B. These correct for the delocalization of positive charge on an atom (A) through neighboring electron density from adjacent A-H bonds and A-B bonds, respectively. Cationic reactions also necessitated corrections for the removal of an electron from an atomic orbital. These included IP_P3p_A/M and IP_P2p_M for the removal of an electron from a paired 3p or hybrid 3p orbital in a free atom or molecule and from a paired 2p hybridized orbital in a molecule, respectively. Lastly, anionic reactions required corrections for the addition of an electron to an unpaired 2p orbital on an atom (EA_AO_U2p) or to the molecular orbital of first row atom with a localized radical and no adjacent multiple bonds (EA_R1_noMB).

The parameters from the IP/EA model[2b] are used in the present work without any modification. As is noted below, there are a few special cases (such as azides) where defining new parameters would likely reduce errors. In spite of this, we do not believe that the current data set is sufficiently large or diverse to justify such development at this time. As more data becomes available (via either experiments or calculations), increases in the number of parameters can be considered.

II.C. Transition metals

The B3LYP-LOC methodology has also been successfully extended to transition-metal containing systems[2d], in which a data set of 36 experimental atomic energies and 71 bond dissociation energies were employed. Sets of 10 and 21 parameters were built to correct for atomic energy and bond dissociation energy errors, respectively, resulting in an MUE decrease from 7.7 to 0.4 kcal/mole for atomic data and 5.3 to 1.7 kcal/mole for bond dissociation data. This initial model is based upon a wide range of excitation energies, ionization potentials, and bond energies gathered from experimental gas phase measurements. Coupled cluster calculations on transition metal species can be problematic; nonetheless we provided benchmark coupled cluster calculations that agreed reasonably well with experiment for various metal diatomic species. Further, this work shows that the dominant sources of error are qualitatively analogous to those identified in the previous B3LYP-LOC publications2a–c, and corrects for them accordingly, employing phenomenologically similar reasoning.

While the results contained within this work on transition metals are highly encouraging, they do not represent a complete treatment of transition metals containing systems. As most gas phase bond energy data exists primarily for metals in their neutral state or as singly charged cations and metals with low coordination numbers, the dataset was limited to these types of systems. Obviously, a more complete treatment should include transition metals with higher coordination numbers and oxidation states, these being highly common in various biological systems. However, we reserve this endeavor for a subsequent publication. The present paper does not consider any transition metal containing reactions, although such systems will be examined in future efforts.

II.D. Enthalpy of reaction

The most recent B3LYP-LOC work[2c] demonstrates that this methodology is robust across different basis sets [6–31G*, 6–311++G(3*df*,3*pd*), cc-pVTZ, and aug-cc-pVTZ] and reaction types (atomization reactions and molecular reactions). This work further demonstrates a reduction in the MUE from 4.7 to 0.8 kcal/mole over B3LYP for a test set of 70 molecular reactions [at the B3LYP-LOC/6–311++G(3*df*,3*pd*) level]. Our series of works2 show that the systematic errors native to B3LYP make it particularly well suited to the LOC scheme. Importantly, some modern functionals perform noticeably better than B3LYP. Even so, their

errors, still being non-negligible, are more random and hence harder to treat by such trivially-defined parameterizations. Several well-known functionals (SVWN, BLYP, BPW91, etc.) were investigated in this regard. Furthermore, the modern M05-2X[16] and M06-2X[17] functionals were also combined with the LOC scheme. While uncorrected B3LYP is outperformed by M05-2X, which is in turn outperformed by M06-2X, neither of these new functionals integrates as favorably with the LOC methodology as B3LYP for calculation of reaction enthalpies. While non-trivial improvements in performance are seen for M05-2X-LOC and M06-2X-LOC (where the LOC parameters are optimized for each functional individually) over uncorrected M05-2X and M06-2X, they are both consistently outperformed by B3LYP-LOC, which makes it the best method of the three for computing reaction enthalpies. This is not to imply that B3LYP is an inherently better functional than M05-2X or M06-2X when all are in their uncorrected forms. Nor does it imply that other functionals we have not yet tested might produce better results than B3LYP when combined with our LOC methodology. This is a point we intend to examine in future publications. Further, we have provided a complete prescription in this publication and the others[2a–d] for application of our LOC scheme such that other researchers may investigate our LOC scheme with other functionals if they so desire.

On that note, we have not yet explored the possibility of coupling our LOC scheme with various screened hybrids such as the Heyd-Scuseria-Ernzerhof (HSC) functional[24] for the treatment of large molecules. Nonetheless, this presents a promising approach to further treating systematic errors found in DFT, as screened hybrids attenuate those errors found at relatively long length scales (> 5 Å) and our LOC approach corrects for those at shorter length scales. We reserve this endeavor for future publications.

In order for a method to be physically viable, optimal results should emerge as the basis set is converged. This convergence is observed for the B3LYP-LOC approach; the MUE is, in fact, decreased as the basis set size is increased. This represents substantive evidence for the chemical validity of the LOC methodology and interpretation.

Importantly, this most recent work is the first instance in which an automated protocol is employed to assign the LOC parameters and corrections, in contrast to the hand assignments performed in previous works. Specifically, for any reaction given in SMILES format, the total correction to its reaction enthalpy is computed automatically according to the valence bond structure given. This is an important step forward in the process of making the methodology automated and accessible to a wider audience.

II.D.1. Enthalpy of reaction for neutral reactions—The LOC-corrected enthalpy of reaction can be calculated in a straightforward fashion using the standard B3LYP-LOC parameters and is done just as in reference [2c]. The sum of the corrections for the reactant(s) is subtracted from the sum of corrections for the product(s) and this total correction is then added directly to the B3LYP enthalpy of reaction to yield the B3LYP-LOC enthalpy of reaction.

II.D.2. Enthalpy of reaction for ionic reactions—Imagine an anionic S_N2 reaction:

$$Nu^- + R-LG \rightarrow LG^- + R-Nu$$
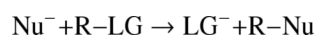
where Nu, R-LG, and LG represent the nucleophile, electrophile, and leaving group, respectively. This may equivalently be written as a series of reactions:

a. $Nu^- \rightarrow Nu° + e^-$

b. $R\text{-}LG \rightarrow R° + LG°$

c. $R° + Nu° \rightarrow R\text{-}Nu$

d. $LG° + e^- \rightarrow LG^-$
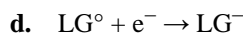
Reaction (a) and (d) are described by the electron affinity of Nu° and LG°, respectively. Electron affinity is defined as

$$EA(X°) = energy(X°) - energy(X^-) \qquad (1)$$

for the reaction

$$X° + e^- \rightarrow X^- \qquad (2)$$

Note that this thermodynamic property is defined as energy (reactants) – energy (products), opposite from other thermodynamic properties, which are defined as energy (product) – energy (reactant).

Each of these sub-reactions will have associated with it a certain correction due to adding or removing an electron. Specifically,

a. $corr(Nu°) - corr(Nu^-) + corr(EA, Nu°)$

b. $corr(R°) + corr(LG°) - corr(R\text{-}LG)$

c. $corr(R\text{-}Nu) - corr(R°) - corr(Nu°)$

d. $corr(LG^-) - corr(LG°) - corr(EA, LG°)$

For reaction (a), the EA correction is *added* to the other terms. While reaction (a) does not match (2) in form, its reaction enthalpy does match that of (1), therefore the EA correction should be *added* to the other terms. Conversely, the enthalpy for (d) is defined opposite that of (1) and therefore the EA term is *subtracted* from the others. Note that reactions (b) and (c) contain only neutral species and are therefore completely described by the original suite of LOC parameters.[2a]

Combining all the corrections for (a) – (d) gives a total correction

$$corr(anionic,\ SN2) = corr(R-Nu) + corr(LG^-) - corr(Nu^-) - corr(R-LG) + corr(EA,\ Nu°) - corr(EA, LG°)$$

Obviously this is not limited in application to just anionic S_N2 reactions, but can be applied to all anionic reactions. Also, cationic reactions are treated by the following formula using the same logic

$$corr(cationic,\ SN2) = corr(R-Nu^+) + corr(LG{:}) - corr(R-LG^+) - corr(Nu{:}) + corr(IP, Nu{:}) - corr(IP, LG{:})$$

III. Development of a B3LYP-LOC model for barrier heights

III.A. Overview

The B3LYP-LOC methodology has been well described for ground states[2a–d]; but it has yet to be applied to transition states. As a first approximation, we assume, for purposes of estimating the valence bond states needed to assign correction parameters, that all transition states lie exactly mid-way along the reaction coordinate connecting product and reactant. Specifically, if a bond has order 1 (single bond) in the reactant and order 2 (double bond) in the product, it is assigned a bond order of 1.5 in the transition state. Similarly, an atom with hybridization sp^3 in the reactant and sp^2 in the product is assigned a hybridization of $sp^{2.5}$ in

the transition state. Obviously this assumption is crude and likely to lead to less than optimal results in many cases. Therefore, it is desirable to develop a continuous functional form of the B3LYP-LOC correction such that the entire reaction coordinate may be mapped, better accommodating asynchronous transition states. Yet, we reserve this for a subsequent publication and use the approximation here to show the validity, applicability, and power of the model, even in its crudest form.

Where possible, the previously developed B3LYP-LOC parameters are assigned to the transition state. For example, a carbon-carbon bond that maintains its bond order in the reactant and transition state will be assigned the standard parameter, MSBC (medium single bond correction), in both. After assigning these parameters, parameters specific to transition states must be assigned. These new parameters are given in Table 1.

The environmental single bond correction (ESBC) was previously described2a,c. Yet, it is included in Table 1 as its definition has been modified so that it can be applied in an automated fashion to the transition states as well. As previously defined, ESBC is applied additively for every single bond A-B (where neither A nor B is fluorine or hydrogen, nor is the single bond part of a three- or four-membered ring) with a neighboring single bond, A'-A-B (A' not fluorine or hydrogen). In this most recent implementation, for every A-B bond with approximate bond order $n + 0.5$ (n=0,1), with neighboring bond A'-A, 1 ESBC is applied if A'-A is a single bond. Likewise, only 0.5 ESBC is applied for A'-A having approximate bond order $n + 0.5$ (n=0, 1). The original restriction applies in that A-B, regardless of bond order, cannot be a bond in a three- or four-membered ring. This is presumably because the bond angles in these three- or four-membered rings are too small to appreciably allow for electronic excursions that ESBC was designed to treat. Therefore, transition states which also display this same characteristic small bond angle ($< 94.0°$) do not receive ESBCs either. Specifically, consider four atoms connected by single bonds, A-B-C-D. If bond angle ABC is $< 94.0°$, neither bond AB nor bond BC may count as a base orbital for ESBCs. Yet, bond CD is still treated in the normal fashion – receiving 1 ESBC for its neighboring BC bond. Via this rational, the bonds of the bridge in the transition states for reactions 2 and 3 in addition to all bonds of the partial 3- or 4-membered rings in the transition states for reactions 8, 10, 101, and 102 were not assigned ESBCs.

After assigning all the corrections to the reactant and transition states, the difference in these corrections may then be applied directly to the B3LYP barrier height to obtain the B3LYP-LOC barrier height in an additive fashion. This is straightforward for neutral reactions. Anionic and cationic reactions require one additional correction each and are discussed in the following sections.

The original B3LYP-LOC scheme[2a] provides corrections for various hybridization states of atoms, including N/P_sp, N/P_sp^2, etc. The transition state parameters unsurprisingly take on similar values to these previously defined ones. For example, **$N/P\_sp^{1.5}$** has a value of 4.47 kcal/mole which is similar in value to that of N/P_sp^2, at 4.31 kcal/mole[v]. **$N/P\_sp^{2.5}$** (4.03 kcal/mole) is intermediate in value between N/P_sp^2 and N/P_sp^3 with values of 4.31 and 3.00 kcal/mole[v], respectively. It is not necessarily true that the parameter $N/P\_sp^{n.5}$ must be intermediate in value between that of N/P_sp^n and N/P_sp^{n+1} for it to be physically viable; the formation of a transition state is a complex change in electronic structure in which various competing factors will play a role in determining the error in the original B3LYP calculation, and the empirical corrections absorb all of these effects simultaneously. The original DFT-LOC paper emphasized the transformation of the lone pair in atomic nitrogen from the more localized 2s orbital to a significantly more extended sp, sp^2, or sp^3 hybridized orbital, as a qualitative rationalization of the overbinding associated with achieving the standard hybridization states for nitrogen. Yet, when a transition state is formed, the first shell of neighboring atoms, and their distance distribution, differs from any ground state, and the effects

so introduced can modify the observed DFT error, in a direction that is not easy to infer from the structural transformation. Finally, the original B3LYP-LOC work treats nitrogen and phosphorus equally, finding no appreciable degradation in performance upon combining the two. This is easily justified by the similarity of phosphorus and nitrogen in electronic structure. Accordingly, we have chosen to combine the corresponding nitrogen and phosphorus corrections into $N/P\_sp^{n.5}$. Although there are no cases of phosphorus atoms that fit into the $N/P\_sp^{1.5}$ category and only one transition state with phosphorus that fits into the $N/P\_sp^{2.5}$ category, we assert this is a likely categorization for any possible future occurrences based upon the precedence set in the previous work.[2a]

Like the transition state parameters for nitrogen of intermediate hybridization, **$O\_sp^{2.5}$** (2.02 kcal/mole) is similar in value to the previously defined parameters, O_sp^2 and O_sp^3, which have values of 0.95 and 1.67 kcal/mole, respectively.

MSBC/LSBC_0.5 (−1.82 kcal/mole) also has a value similar to those originally defined for MSBC and LSBC, −1.92 and −2.49 kcal/mole,[(v)] respectively. The original B3LYP-LOC work[2a] shows a clear correlation between the ratio of orbital size to bond length and the corresponding correction for each bond. Specifically, the corrections for heavy atom pair short single bonds (SSBC), medium single bonds (MSBC) and long single bonds (LSBC) are −1.26, −1.92, and −2.49 kcal/mole,[v] respectively. The longer bond length relative to the orbital size bestows a greater nondynamical correlation energy onto the electron pair in the longer bond than would be if the bond were shorter, necessitating a correction of greater magnitude. We see that the value for MSBC/LSBC_0.5 is smaller than both MSBC and LSBC in magnitude, despite the fact that the bond length is clearly larger. Yet, while the bond length is larger for such "half bonds", the orbital size also experiences a concomitant increase in size (with respect to "full" single bonds). Consider for example the reaction $H_2C=CH_2 + CH_3° \rightarrow H_2C°\text{-}CH_2\text{-}CH_3$. While the "half bond" between the ethene and methyl in the transition state is longer than the corresponding single bond, its orbital size is also larger. Whereas the corresponding C-C bond is comprised of two sp^3 orbitals, this "half" bond is comprised of two orbitals intermediate in hybridization between pure p orbitals (as in the reactants) and sp^3 orbitals (as in the products) making it comparatively larger. Accordingly, the ratio of orbital size to bond length does not vary greatly between the "full" medium and long single bonds and the medium and long single "half" bonds.

A second argument (not contradictory to the discussion above – the final parameter value reflects both chemical effects in combination) is that, as any bond is driven to infinite separation, the correction parameter for the bond must go to zero. When atom B is infinitely far from atom A, excursions of the now unpaired electrons on atom A toward atom B (and *vice versa*) no longer deviate from those seen in an atom; thus, the estimate of the two particle correlation function by the DFT functional cannot be presumed to have the systematic error inferred for C-C, C-Cl, etc., bonds. At what point the correction term peaks cannot be rigorously determined without performing accurate high level *ab initio* computations of the full bond breaking curve and comparing the DFT results, but it seems reasonable to propose that the maximum in fact occurs close to the equilibrium bond length, and prior to the length associated with the transition state structure (at least in a typical transition state; early transition states might exhibit a systematically different trend, a subject we leave to future investigation). The fact that we are able to combine the MSBC and LSBC parameters here (no transition state bond would be characterized as "short"), and that the value obtained is smaller than the MSBC equilibrium value, provides strong evidence that this hypothesis is correct. This transition state bond correction parameters is employed in virtually every molecule in the training set, and there is often more than one bond per test case; thus, the value of the parameter has a major

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[(v)]For the 6–311++G(3*df*,3*pd*) basis set, for example

effect on the average error. The successful use of a single parameter for all single bonds between heavy atoms in the transition state, and the low average error and number of outliers obtained by doing so, provides confidence that this parameter is not overfit, as does its chemically consistent, readily interpretable value (per the two arguments made above).

The parameter **AA_1.5** is applied for all bonds of approximate bond order 1.5. Its value (−0.36 kcal/mole) is similar to the value for double bonds (−0.53 kcal/mole)[v], reflecting the fact that correlation between multiple orbitals in a bond exerts a substantial effect on the correction term (in a fashion that is more difficult to dissect than the corresponding effects for single bonds). This value most likely corresponds to the reorganization of electrons from the localized p orbitals of the double bond to the localized sp^n bonds. The precise value obtained, while thus more difficult to interpret than the transition state single bond value, is at least reasonable. More test cases will be required to investigate whether the fitted parameter obtained here is unduly influenced by the specific set of bonds with bond order 1.5 found in transition states for the current data set.

Similarly, **AA_2.5**, with a value of −0.91 kcal/mole, is employed for all bonds with approximate bond order 2.5. The original B3LYP-LOC work gives optimized values of −0.53, −1.31, and 1.51 kcal/mole[v] for double bonds (DBC), nonpolar triple bonds (TBNPOL) and polar triple bonds (TBPOL), respectively. As in the case of AA_1.5, an obvious rationale for this parameter's exact value is lacking. Notably, this correction is employed many times for the dipolar cycloaddition reactions with azides. In fact, this parameter is employed exclusively for the treatment of dipolar cycloaddition transition states with the lone exception of the transition state for reaction 55 and 56, carbon radical reactions. Accordingly, this parameter may in actuality be capturing effects unique to the azides employed in the dipolar cycloadditions (which present a challenge for localized treatments due to their nonlocal nature) rather than a characteristic of bonds with approximate order of 2.5. Further investigation will be necessary to determine just how general this parameter is, and whether additional parametrization is necessary for other chemistries containing transition state bonds intermediate between double and triple bond character. In contrast, we have much more confidence in the MSBC/LSBC_0.5 bond parameter, which covers many different chemistries, as discussed above.

All hydrogen-hydrogen bonds of approximate bond order 0.5 are assigned the parameter **HH_0.5** (0.55 kcal/mole). The previous B3LYP-LOC work[2a] defined a special parameter for diatomic hydrogen with a value of 0.25 kcal/mole. The value for HH_0.5 is larger despite the fact that it will necessarily vanish as the bond order approaches zero. The reason for this is clear if one considers the relevant transition states, such as that of the reaction $H + H_2 \rightarrow H_2 + H$ for example.[18] These transition states are highly analogous to the well-described H_2^+ molecule.[11] In such cases, approximately one electron is shared between the two hydrogen atoms. Here the self-interaction term does not serve to model nondynamical correlation, but instead engenders a clear source of systematic error.[3] Further, the magnitude of this error becomes larger as the bond is stretched. It is for this reason that the value of the HH_0.5 parameter is larger than that of the value assigned for diatomic hydrogen alone.

The importance of environmental correction terms has already been noted. For example, in a doubly occupied localized orbital, one electron might make excursions into the area of other localized orbitals in order to avoid the second electron of the same orbital. Accordingly, the availability of neighboring bonds to accommodate such excursions is included in the B3LYP-LOC scheme via introduction of the environmental single bond correction, **ESBC**. While not as prevalent, such excursions are also possible in the partial bonds of transition states. Accordingly, excursions into partial bonds of approximate bond order 0.5 and 1.5 are treated with 0.5 ESBC corrections. Of course, the coefficient of 0.5 for the ESBC correction reflects the assumption that the transition state lies exactly midway along the reaction coordinate and

can be fine-tuned to reflect exact transition state location in the continuous implementation of the correction scheme, reserved for future work. Environmental bond corrections are not applied for double or triple bonds. Accordingly, partial environmental corrections for partial bonds transition states are only applied for bonds of approximate order 0.5 and 1.5.

The original B3LYP-LOC work defined a parameter for any hypervalent atom, **OCT_EXP**, such as seen in ClF_3. The large value of this parameter compensates for a very substantial overestimation of nondynamical correlation in these highly electron dense systems. Notably, this same parameter accurately describes the pseudo-pentacoordinate transition state of the S_N2 reaction. Here a hypervalent carbon atom is coordinated to five different atoms with a concomitant increase in electron density and overestimation of nondynamical correlation analogous to that of the ClF_3 case, for example. Accordingly, all transition states with hypervalent non-hydrogen atoms (only S_N2 reactions on carbon centers in this work) are assigned this parameter.

While hypervalent heavy atoms of the transition state receive the OCT_EXP parameter, hypervalent hydrogen atoms receive the **H_dival** parameter. Interestingly, both OCT_EXP and H_dival are similar, taking on values of 3.54 to 4.64 kcal/mole (depending upon basis set) and 3.79 kcal/mole (independent of basis set), respectively. This similarity is not fortuitous, as these parameters arise from the same phenomenon: overestimation of nondynamical electron correlation due to localized high electron density. Accordingly, the H_dival parameter is only assigned when the hydrogen atom is flanked by at least one atom that is neither hydrogen nor carbon. This leads to a clear improvement in performance and can be justified based upon consideration of the virtual orbitals. Transition states in which the hydrogen atom is flanked by only carbon and/or hydrogen atoms, such as CH_3---H---CH_3, are well described without consideration of virtual orbitals. In molecules such as CH_4 and H_2, where the HOMO-LUMO gaps are larger(vi), the virtual orbitals do not contribute substantially to a complete description of the electronic state. Accordingly, B3LYP does not produce substantial errors in describing such systems. Nevertheless, transition states in which a hydrogen atom is sandwiched between at least one atom other than hydrogen or carbon, such as HO---H---CH_3, have a much larger error. Because the HOMO-LUMO gap in these heavy atoms (O, P, N, S, etc.) is smaller(vii), excitations of electrons in the heteroatom lone pairs into these virtual orbitals make a more significant contribution to the electronic state. The octet expansion parameter (OCT_EXP) is interpreted similarly; B3LYP does not accurately capture the effect of virtual orbitals for hypervalent atoms, leading to the large errors seen in these cases. In essence, hypervalent compounds cannot place all of their valence electrons into the standard valence shell orbitals and accessing virtual lone pair orbitals in the first shell of atoms around the central atom (or in the central atom itself) is the most economical means of distributing electrons in structures of this type. The low energy gaps of such states then appear to cause problems for B3LYP, leading to overbinding of the corresponding structures.

III.B. Barrier height corrections for anionic transition states

Consider the anionic S_N2 reaction
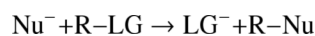
$$Nu^- + R-LG \rightarrow LG^- + R-Nu$$

where again, Nu, R-LG, and LG refer to the nucleophile, electrophile and leaving group, respectively. Here, the corrections to the transition state are applied in the usual fashion. Yet, another parameter is added to the calculated barrier height to account for the negative charges

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(vi)11.7 eV for methane at the B3LYP/cc-pVQZ(-G) leve

(vii)8.9 and 8.0 eV for water and ammonia at the B3LYP/cc-pVQZ(-G) level, respectively

$$corr(BH) = 0.5 [corr(EA, Nu^\circ) + corr(EA, LG^\circ)]$$

The coefficient of 0.5 is added to reflect the assumption that the negative charge in the transition state is equally distributed between the Nu and the LG. The above equations follow readily from equation (3). Obviously the parameter of 0.5 can be tuned to reflect the location of the transition state along the reaction coordinate; earlier transition states weighing the term corr (EA, LG°) more heavily and later transition states weighing corr(EA, Nu°) more heavily. This is reserved for subsequent publication in which a continuous functional form is developed.

III.C. Barrier height corrections for cationic transition states

Analogously, imagine a cationic S_N2 reaction
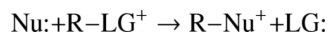
$$Nu: + R-LG^+ \rightarrow R-Nu^+ + LG:$$

where again, Nu, R-LG, and LG refer to the nucleophile, electrophile and leaving group, respectively. Here, the barrier height also receives an additional correction derived from equation (6) where the assumption is made that half of the positive charge resides on the Nu while the other half resides on the LG in the transition state.

$$corr(BH) = 0.5 [corr(IP, Nu:) + corr (IP, LG:)]$$

Just as with anionic transition states, the coefficient of 0.5 can be tuned once a continuous functional is developed.

III.D. Computational methods

All stationary points (reactants, products, and transition states) were optimized at the UB3LYP/ 6-31G* level using the JAGUAR *ab initio* quantum chemistry code19. Vibrational frequencies were also calculated and scaled by 0.9806 (as suggested by Scott and Radom20) to obtain the zero point energy (ZPE) and enthalpy of each species. Single point calculations were then performed at the $6-311++G(3df,3pd)$ level for neutral and cationic reactions and cc-pVTZ++ level for anionic reactions. The total enthalpy of each species x (H_x) was then taken as the sum of the SCF energy computed in the higher basis [$6-311++(3df,3pd)$ or cc-pVTZ++] and the enthalpy and ZPE computed in the $6-31G*$ basis. The uncorrected B3LYP reaction enthalpy is then given by

$$\Delta H_{rxn,B3LYP} = \Delta H_{product} - \Delta H_{reactant}$$

The uncorrected B3LYP barrier height is also given by

$$\Delta H^{\ddagger}_{B3LYP} = \Delta H_{transition \ state} - \Delta H_{reactant}$$

(Note that in many publications barrier height is used interchangeably with Arrhenius activation energy. It is important to recognize that these two quantities differ by a factor of nRT. Barrier height is used exclusively here.)

From these, the B3LYP-LOC reaction enthalpy and barrier height are readily obtained by a simple correction term

$$\Delta H_{rxn,B3LYP-LOC} = [\Delta H_{product} + corr_{product}] - [\Delta H_{reactant} + corr_{reactant}] = \Delta H_{rxn,B3LYP} + corr_{product} - corr_{reactant}$$
$$\Delta H^{\ddagger}_{B3LYP-LOC} = [\Delta H_{transition\ state} + corr_{transition\ state}] - [\Delta H_{reactant} + corr_{reactant}] = \Delta H^{\ddagger}_{B3LYP} + corr_{transition\ state} - corr_{reactant}$$

Lastly, each of the $corr_x$ terms is obtained simply from the sum of all corrections for species *x*, as assigned from its valence bond structure and given by the full suite of LOC parameters[2a–d]. The reader is referred to the supporting information for additional details and examples.

IV. Results and discussion

The B3LYP-LOC methodology as described in section III was applied to a large dataset of 105 unique barrier heights and 69 enthalpies of reaction for which *ab initio* or experimental data was available. This dataset, shown in Figure 1, is notable for the many different reaction types, including cycloadditions, electrocyclizations, dipolar cycloadditions, S_N2, carbon radical, and hydrogen radical reactions. After applying the original B3LYP-LOC parameters, as previously developed[2a], the new parameters were assigned and their values (shown in Table 1) were determined in a linear-least-squares fashion.

Table 3 summarizes the results of applying the B3LYP-LOC methodology to this large dataset and compares uncorrected B3LYP to B3LYP-LOC. The B3LYP-LOC method performs significantly better than uncorrected B3LYP, with essentially zero additional computational cost. The error in the MUE of the entire dataset is reduced to near-chemical accuracy for both reaction enthalpies and barrier heights. Further, Table 3 shows that the MUE is reduced across nearly all categories for both the reaction enthalpy and barrier height, again often achieving chemical accuracy. This is also shown visually in Figure 2 and Figure 3.

For reaction enthalpies, the MUE is reduced nearly 20-fold for cycloadditions, 6-fold for dipolar cycloadditions, and 4-fold for both carbon radical and electrocyclic reactions. The same trend holds for barrier heights, in which B3LYP-LOC displays up to a 7-fold improvement in MUE over B3LYP.

A few exceptions exist, in which B3LYP-LOC displays greater error than B3LYP. These include the enthalpy of S_N2 reactions and barrier heights for electrocyclizations and sigmatropic shifts. While B3LYP-LOC performs less favorably than B3LYP for the S_N2 reactions, this degradation is relatively small in magnitude, especially when compared to the remarkable improvement displayed by the other reactions subcategories when employing B3LYP-LOC. It is also true that B3LYP outperforms B3LYP-LOC when calculating barrier heights for both electrocyclizations and sigmatropic shifts. Yet, because of the limited availability of benchmark data, both of these reaction subcategories only contain three reactions each. Further, B3LYP, perhaps fortuitously, performs anomalously well for these small datasets. Therefore, additional reactions within these subcategories should be investigated once benchmark data becomes available to truly gauge B3LYP-LOC's performance for these reaction types.

One particular type of chemistry requires some explicit comments. Our dataset contains several azides: hydrazoic acid (N_3H), methylazide (N_3CH_3), formylazide (N_3CHO), phenylazide ($N_3C_6H_5$), and methane sulfonylazide ($N_3SO_2CH_3$). Each of these possesses at least the two unique resonance forms shown in Figure 4. Therefore, we must decide upon one resonance structure for each in order to successfully apply the LOC scheme.

Ab initio or experimental enthalpies of formation can be located for only hydrazoic acid and methylazide.[21] Comparing the *ab initio* numbers to those computed with B3LYP-LOC shows clearly superior performance when resonance structure (a), as opposed to (b), is utilized. As argued in ref. [2a], B3LYP-LOC analysis can be viewed in difficult cases like this one as implying the dominance of a particular resonance structure.

With this in mind, all azides were assumed to have the resonance structure (a). Yet, other resonance structures need to be considered for some other azides. Specifically, in accordance with previous B3LYP-LOC work[2a], methane sulfonylazide is taken as shown in Figure 5.

Lastly, formylazide requires even further analysis. We propose that it deviates from resonance structure (a) and instead adopts the form shown in Figure 6. We make this assertion given that the reaction enthalpy MUE of the formylazide-containing reactions drops from 2.6 or 3.5 kcal/mole to 1.2 kcal/mole using this structure. One can also argue that this is the best resonance structure as the negative charge is localized on the most electronegative element. It should also be noted that this molecule was assigned a charge transfer (CT) parameter.

In conclusion we recommend that resonance structure (a) be employed for all azides N_3R unless the negative charge may be delocalized through the R group to a more electronegative element than nitrogen when employing structure (b). Note that phenylazide was treated successfully with resonance structure (a) despite the fact that (b) would allow for delocalization of charge through the phenyl ring. Arguably, such a charge delocalization is not the dominant resonance structure and a phenyl group does not play the same role as the aldehyde.

Unfortunately, while Mulliken charge analysis was employed to probe for dominant resonance structures for all of these azides, the results were highly inconclusive as they depended highly on basis set and did not seem to converge with higher levels of theory. This dependence is entirely consistent with the observations of other researchers.[23] Accordingly, no conclusions were drawn from this data.

In general, any successful parameterization method must guard against over-fitting. We put forward that the large data set employed (>100 barrier heights) and comparatively small number of parameters developed (eight) makes the possibility of over-fitting small. Nonetheless, to confirm this hypothesis, we have divided the dataset into roughly equal halves, using each half independently as a training set. The parameter values obtained from these two different sets were then applied to the other half of the data to give MUEs of 1.1 to 1.4 kcal/mole. This value should be compared to the MUE derived using the whole dataset as a training set, 1.1 kcal/mole. This provides significant evidence that overfitting is not a major problem, at least as judged by the present data set. As noted above, there may be specific cases where additional parameters will be required as new types of structures are investigated. Lack of transferability, a problem that is fundamentally different from overfitting, can be fully addressed only by using substantially larger and more diverse data sets.

The results for reaction enthalpies presented in Tables 3 require the use of no additional adjustable parameters, and hence can be regarded as a true test set for the B3LYP-LOC methodology developed previously. (All reaction enthalpies and barrier heights are given in the supporting information.) Some of the reactions can be derived from the atomization reactions of the G2/G3 database, and hence cannot be used for this objective. If we consider only reactions that cannot be derived from the G2/G3 atomization reactions (52 in all) the average MUE for B3LYP and B3LYP-LOC enthalpies of reaction are 7.4 and 1.1 kcal/mole, respectively. Note that this B3LYP-LOC reaction enthalpy MUE is identical to the MUE for all reactions (1.1 kcal/mole) and also to the average error for the training set[2a], on the order of 1.0 kcal/mole. Independent of the validity of the transition state parameters we have derived here, these results suggest that, for reaction thermochemistry, B3LYP-LOC will perform at the

level of near-chemical accuracy within its current domain of applicability (molecules composed of first and second row atoms). Furthermore, the largest absolute error in reaction energy is 3.3 kcal/mole, whereas the largest absolute B3LYP error is on the order of 19 kcal/mole (and there is a significant number of reactions with errors of this order of magnitude). The consistency of the methodology, across a wide range of chemical phenomena, and without further parameter adjustment, continues to be a strong aspect of the approach.

For barrier heights, there is only one reaction with error greater than 3.5 kcal/mole. Entry 99, $CH_4 + O$ (triplet) $\rightarrow CH_3 \cdot + \cdot OH$, has a signed error of 6.3 kcal/mole. Interestingly, the B3LYP error for this reaction barrier is 10.6 kcal/mole, the largest such error in the entire data set, and roughly 3–5 kcal/mole higher than that of comparable radical reactions in the database. This observation suggests at least the possibility that there is a problem with the reference data; if the B3LYP error were more in line with other reactions, the B3LYP-LOC error would be much smaller. We plan to follow up on this point in future work. It is of course also possible that at least some of the residual errors are a result of inaccuracies in the reference data as well; unlike the G2/G3 set of atomization energies, it is not possible to put rigorous error bars on the reference data for many of the reactions included here. Nevertheless, the level of agreement, for an initial effort, is quite satisfactory, and encourages us to continue the development of the B3LYP-LOC model along lines discussed in the introduction.

V. Conclusions

The results discussed above confirm that the core B3LYP-LOC approach provides high accuracy results for enthalpies of reaction, and introduce for the first time a viable model for obtaining barrier heights with this methodology. The barrier height results are comparable in accuracy to what is obtained for enthalpies of reaction, and display little fluctuation in performance across a diverse set of transition state structures and reaction chemistry. The ratio of adjustable parameters (8) to new data points (105) is reasonable, and the parameters obtained from fitting are physically consistent with previously developed B3LYP-LOC parameters for ground state thermochemistry.

As indicated above, our next objective is to construct a B3LYP-LOC methodology that is a continuous function of the coordinates. Now that we have parameters for the key stationary points, this should be straightforward. We also intend to assemble a substantially larger data set, and to carry out comparisons using this data set with methods such as M06-2X and screened hybrids (in both the original and LOC-corrected forms), which have also shown great promise with regard to reducing DFT errors. Head to head comparisons on large and diverse data sets will enable the strengths and weaknesses of each approach to be examined in detail. Ultimately, adjustment of both additive empirical valence bond type corrections, such as those used here, and intrinsic DFT functional parameters, as has been carried out quite effectively by the Truhlar group, is likely to yield the most accurate and reliable methodology. An effort of this type will require a significant amount of additional work, but does appear to represent a promising path forward for the long run. Further, it should ultimately be possible to extend this methodology to excited states.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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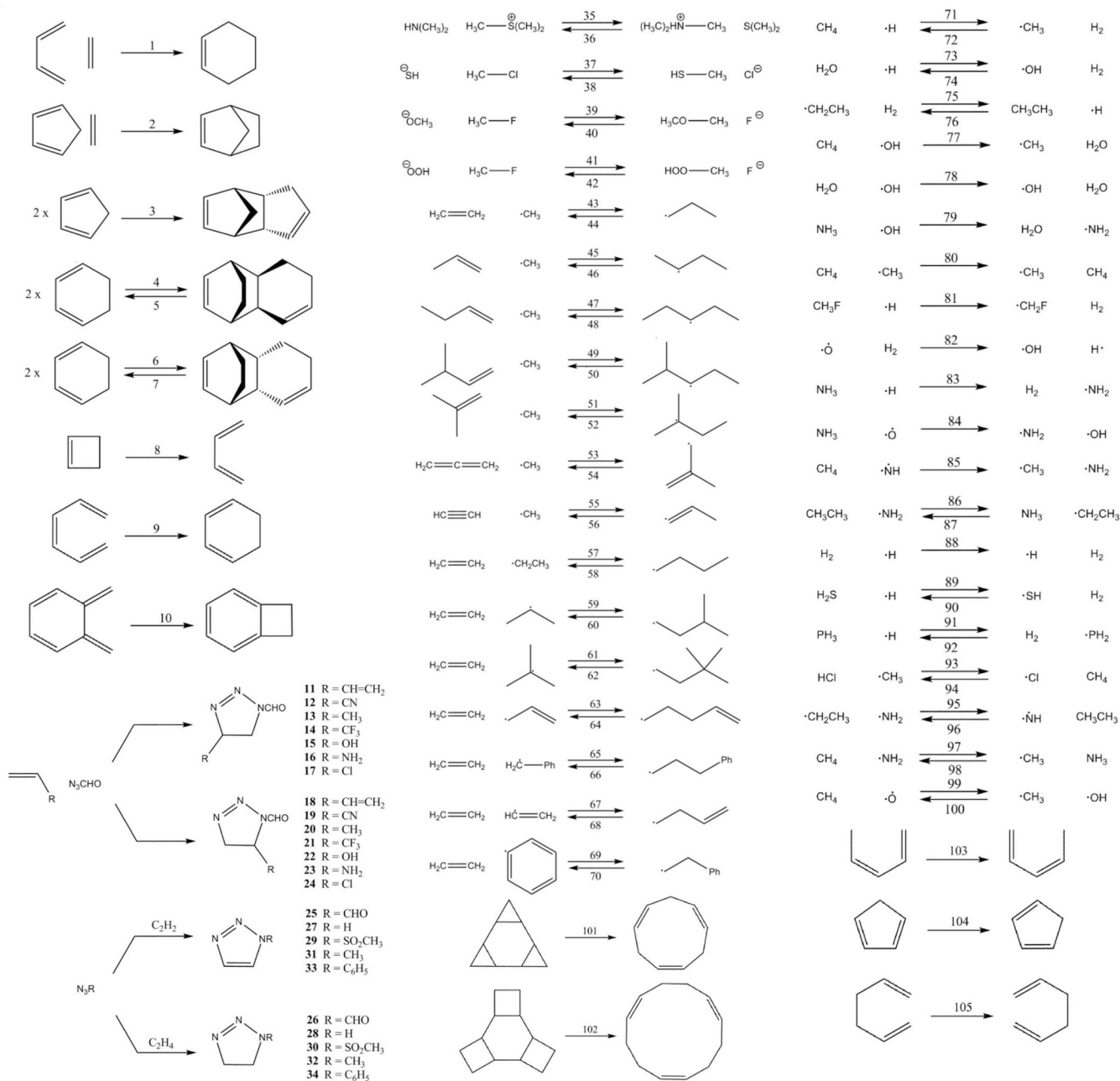24. Heyd J, Scuseria GE. J. Chem. Phys 2004;121:1187–1192. [PubMed: 15260659]
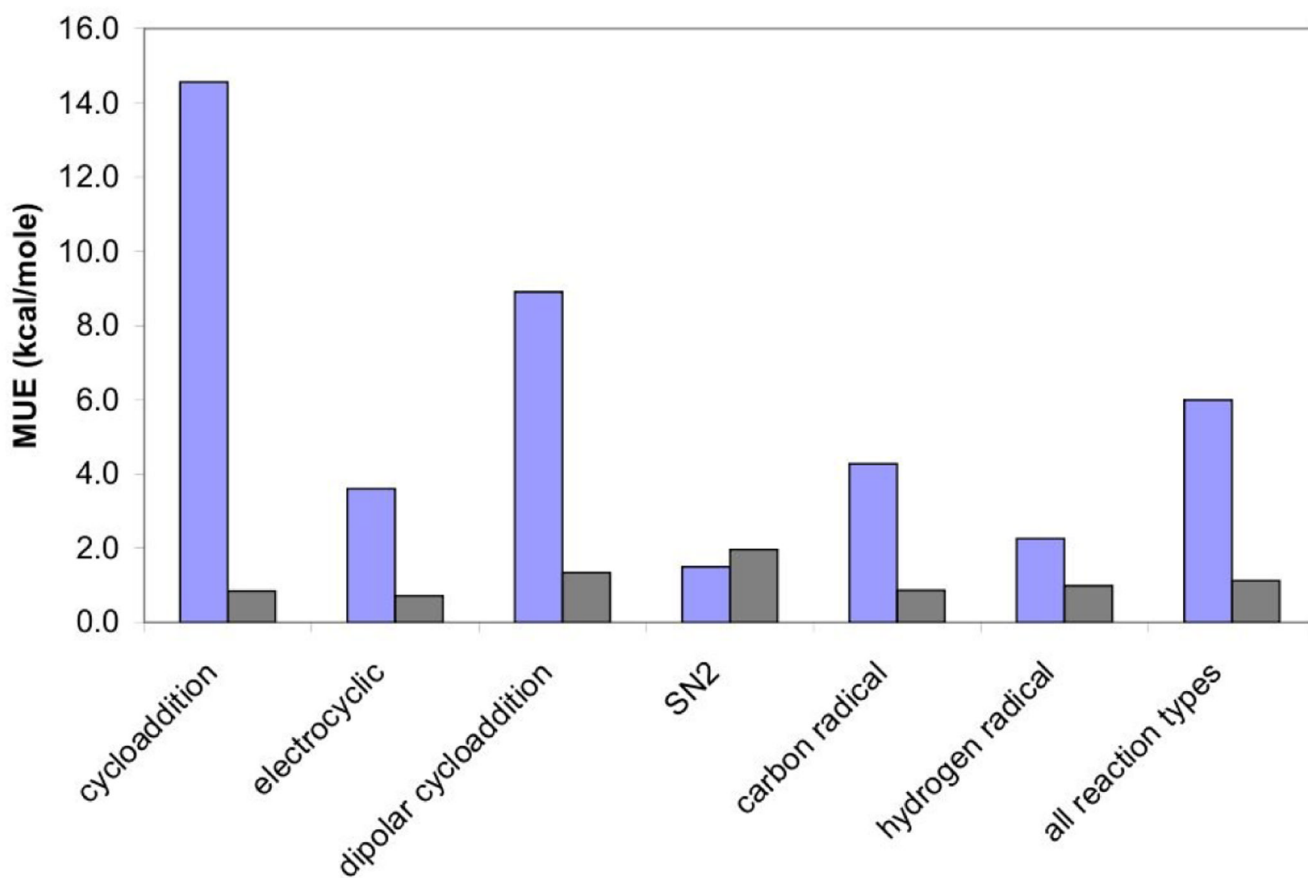
Figure 1.
Reactions of the test set

Figure 2.
Mean unsigned error (MUE) for enthalpy of reaction (ΔH_{rxn}) for various reaction types.
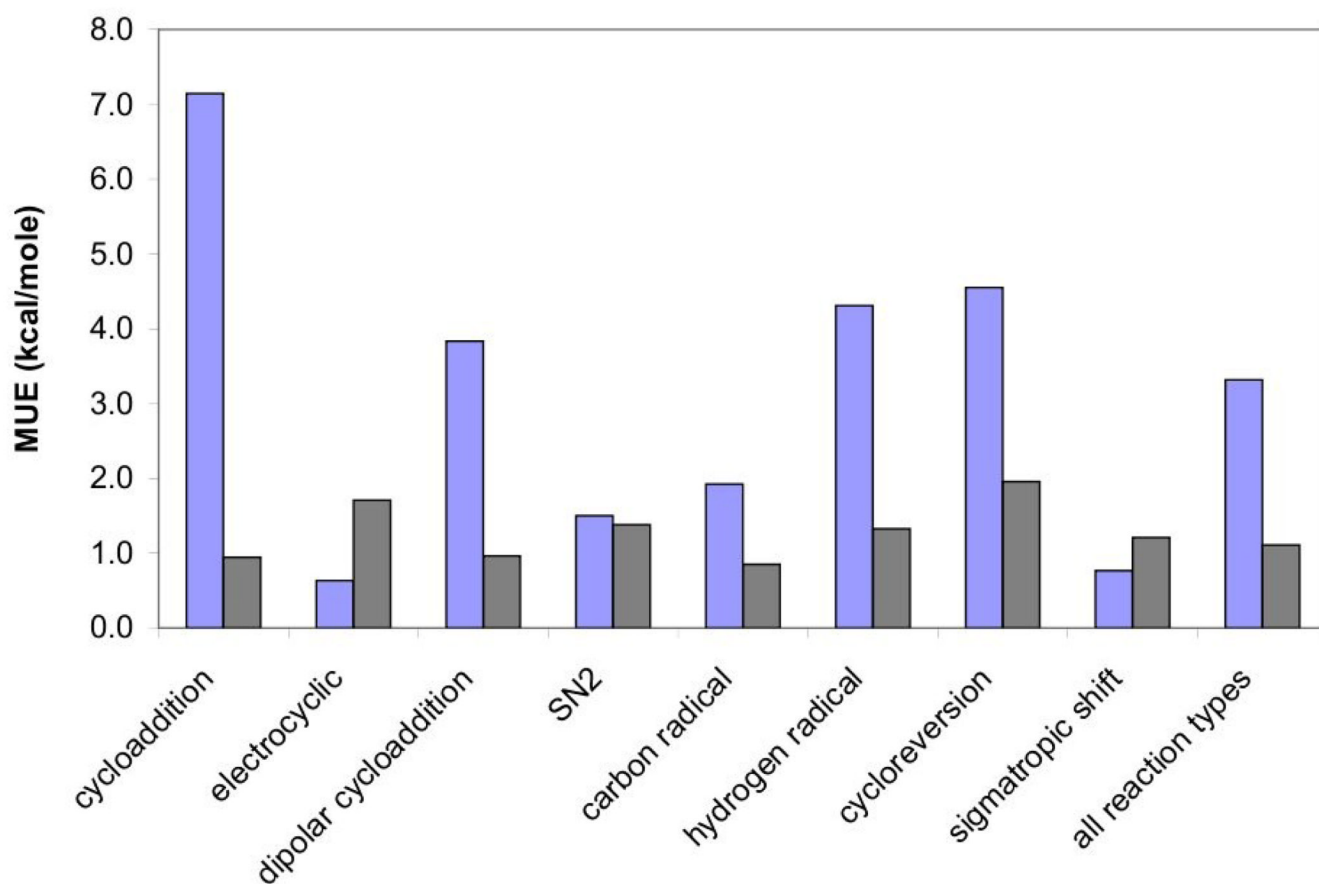B3LYP-LOC is shown in gray while uncorrected B3LYP is shown in blue.

Figure 3.
Mean unsigned error (MUE) for barrier heights ($\Delta H^{\ddagger}$) for various reaction types. B3LYP-LOC is shown in gray while uncorrected B3LYP is shown in blue.
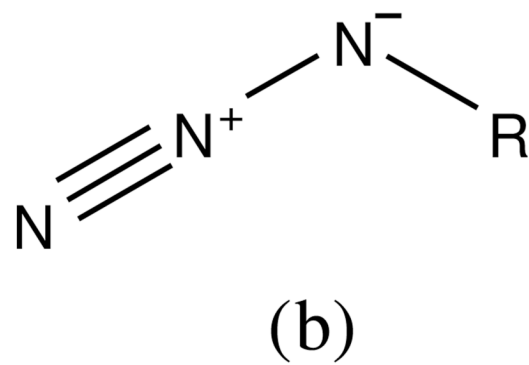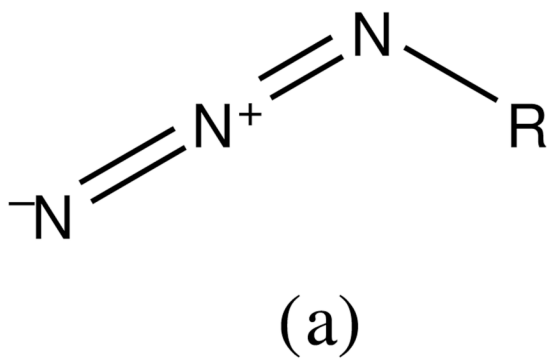
Figure 4.
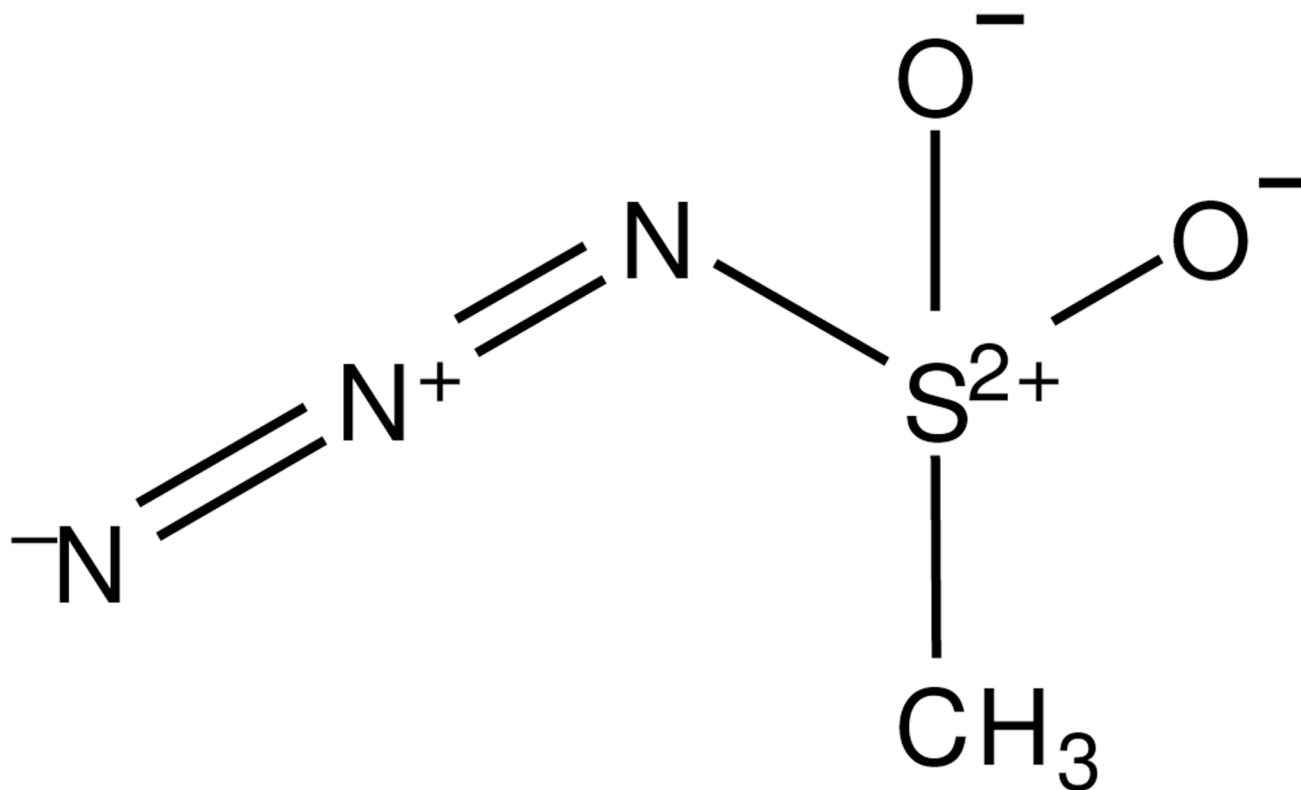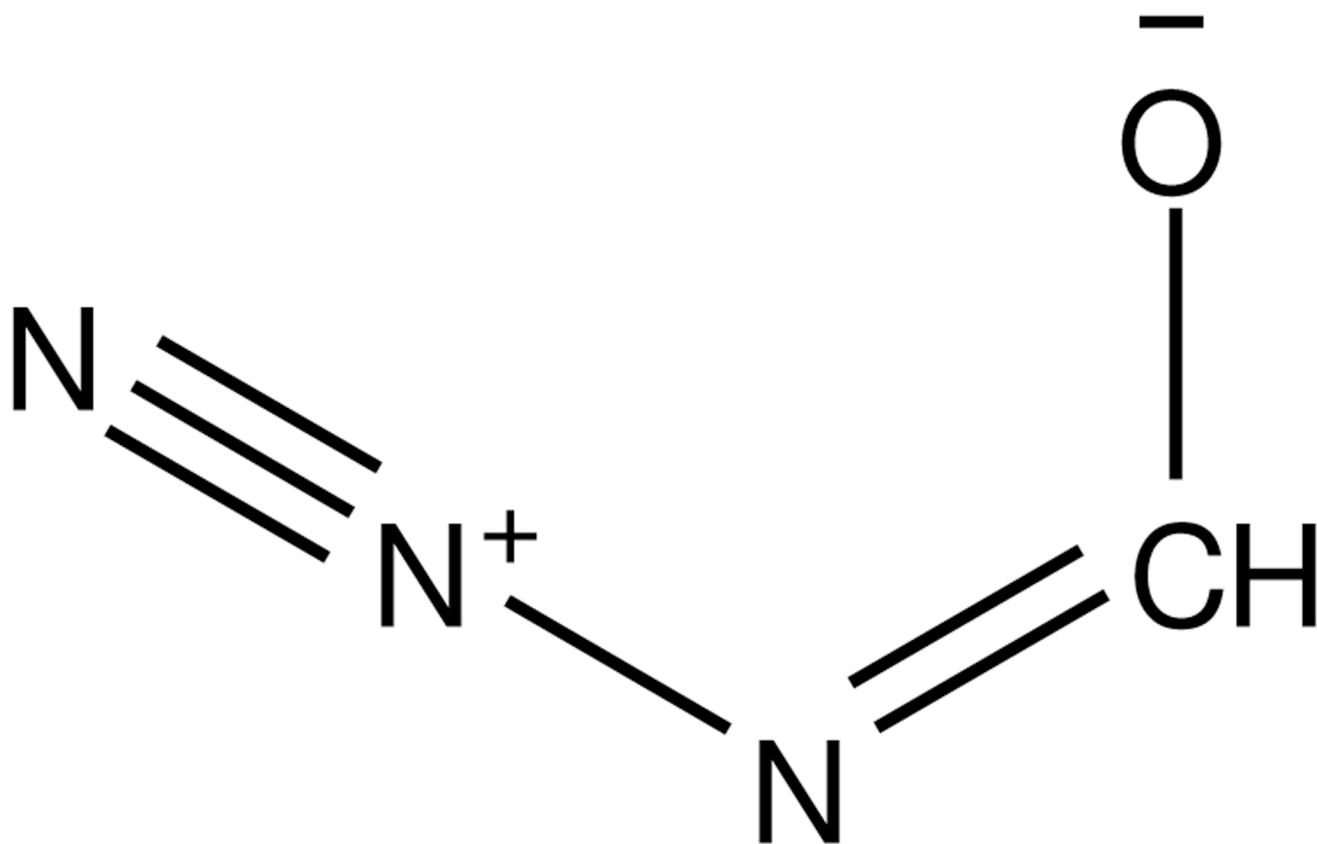resonance structures for a general azide

Figure 5.
methane sulfonyl azide

Figure 6.
formylazide

Table 1

B3LYP-LOC parameters for transition states

Parameter	Description	Value (kcal/mol)
N/P_sp$^{1.5}$	Applied for every N or P atom with hybridization that can be considered partly sp and partly sp^2	4.47
N/P_sp$^{2.5}$	Applied for every N or P atom with hybridization that can be considered partly sp2 and partly sp3	4.03
O_sp$^{2.5}$	Applied for every O with hybridization that can be considered partly sp2 and partly sp3	2.02
MSBC/LSBC_0.5	Applied for every bond of approximate order 0.5 between any atom pairs falling within the description of MSBC and LSBC. Specifically, C---C, C---Cl, N---N, O---O, N---O, F---F, O---Cl, Na---Na, Si---C, S---C, S---O, S---N, any pair of second row atoms other than NaCl	−1.82
AA_1.5	Applied for every bond with approximate bond order 1.5	−0.36
AA_2.5	Applied for every bond with approximate bond order 2.5	−0.91
HH_0.5	Applied for every H-H bond with approximate bond order 0.5	0.55
H_dival	Applied for every transition state in which a hydrogen atom is partly bonded to two atoms, at least one of which is neither carbon nor hydrogen	3.79
ESBC(ii)	Applied for every bond A–B (of order 0.5, 1, or 1.5; where neither A nor B are fluorine or hydrogen, and the bond is not part of a three- or four-membered ring) with neighboring single bond A'-A (where neither A nor A' are fluorine or hydrogen). Likewise, 0.5 ESBC is applied for every neighboring bond A'-A (where neither A nor A' are fluorine or hydrogen) with bond order 0.5 or 1.5 with the same restrictions on A–B stated above.	−0.50(iii) −0.51(iv)
OCT_EXP(ii)	Defined previously for Cl, P, or S atoms that have a valence shell expansion beyond the usual octet. Also applied to any transition state in which an atom (other than hydrogen) experiences an increase in coordination number beyond its octet. This includes the pseudo-penta coordinate transition state of SN2 reactions, for example.	4.92(iii) 3.54(iv)
RH(ii)	Defined previously to apply to every atom on which the localized singly occupied orbital is bonded to a hydrogen atom. Extended here to also apply to any atoms of the transition state with partial radical character. Applied additively for each unpaired electron and each hydrogen.	0.55(iii) 0.34(iv)
RA(ii)	Previously assigned for every atom (of the first or second row) with a localized radical and a single or double bond to another atom. Extended here to include all atoms of the transition state with partial radical character. Applied additively for each unpaired electron and for each bonded first or second row atom.	1.62(iii) 1.71(iv)

(ii)This parameter was first defined in ref. [2a] and here its definition is simply extended to include transition states.
(iii)As defined in ref. [2a] for the 6–311++G(3*df*,3*pd*) basis
(iv)As defined in ref. [2a] for the cc-pVTZ++ basis

(ii)This parameter was first defined in ref. [2a] and here its definition is simply extended to include transition states.
(iii)As defined in ref. [2a] for the 6–311++G(3*df*,3*pd*) basis
(iv)As defined in ref. [2a] for the cc-pVTZ++ basis

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(ii)This parameter was first defined in ref. [2a] and here its definition is simply extended to include transition states.
(iii)As defined in ref. [2a] for the 6–311++G(3*df*,3*pd*) basis
(iv)As defined in ref. [2a] for the cc-pVTZ++ basis

Table 2

Experimental and calculated enthalpies of formation

enthalpies of formation (kcal/mol)	hydrazoic acid	methylazide
Ab initio (G2 theory)	70.4	71.0
B3LYP	59.4	62.1
B3LYP-LOC (a)	71.2	73.1
B3LYP-LOC (b)	65.1	67.1

Table 3

Mean unsigned error (kcal/mole) of ΔH_{rxn} and $\Delta H^{\ddagger}$ calculated with B3LYP and B3LYP-LOC

	ΔH_{rxn}		$\Delta H^{\ddagger}$	
reaction type	B3LYP	B3LYP-LOC	B3LYP	B3LYP-LOC
cycloaddition	14.6	0.8	7.1	0.9
electrocyclic	3.6	0.7	0.6	1.7
dipolar cycloaddition	8.9	1.3	3.8	1.0
S_N2	1.5	2.0	1.5	1.4
carbon radical	4.3	0.9	1.9	0.8
hydrogen radical	2.3	1.0	4.3	1.3
cycloreversion[x]	n/a	n/a	4.6	2.0
sigmatropic shift[xi]	n/a	n/a	0.8	1.2
all reaction types	6.1	1.1	3.3	1.1

[x]Enthalpy of reaction data unavailable.

[xi]Enthlapy of reaction is necessarily zero as the reactant and product are identical.