Theoretical Thermochemistry for Organic Molecules: Development of the Generalized Connectivity-Based Hierarchy

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S *Supporting Information*

ABSTRACT: A generalized, unique thermochemical hierarchy applicable for all closed shell organic molecules is developed in this paper. In this chemically intuitive, structure-based approach, the connectivity of the atoms in an organic molecule is used to construct our hierarchy called "connectivity-based hierarchy" (CBH). The hierarchy has several rungs and ascending up the hierarchy increasingly balances the reaction energy. It requires no prior knowledge of the types of molecules and hybridizations for the appropriate balancing of the bond types and the bonding environments of the atoms. The rungs can be generated by an automated computer program for any closed shell organic molecule, and the first three rungs generate the simplest reactions for the widely used isodesmic, hypohomodesmotic, and hyperhomodesmotic schemes. The generated reaction schemes are unique for each rung and are derived in a simpler manner than previous approaches, avoiding potential errors. This work also suggests that for closed shell organic molecules, the previously well-studied homodesmotic scheme does not have a fundamental structure-based origin. In a preliminary application of CBH, density functional theory has been used to calculate accurate enthalpies of formation for a test set of 20 organic molecules. The performance of the hierarchy suggests that it will be useful to predict accurate thermodynamic properties of larger organic molecules.

1. INTRODUCTION

Electronic structure theory has been widely used to make thermodynamic predictions on organic molecules for over four decades.[1−3] Initially, in an era when sophisticated theoretical methods were not yet developed, accurate methods to compute the bond energies and the thermodynamic properties of organic compounds were not available. Subsequently, introduction of the isodesmic bond separation (IBS) scheme by John Pople in 1970[4−6] enormously improved the accuracy of the predictions using simple theoretical models such as Hartree−Fock theory with moderate basis sets. Pople's IBS scheme illustrated, for the first time, the significance of appropriately balancing reaction energies resulting in substantial error cancellation and yielding better calculated accuracy.

Furthering the ideas developed by Pople, George and co-workers in 1975[7−9] proposed the hybridization-based homodesmotic scheme (HS) of reactions for organic molecules. This scheme sought to improve upon Pople's IBS scheme and was constructed to offer a superior balance of the bond types and the hybridization of the atoms involved. Following this, a plethora of schemes, some of which are called hyperhomodesmotic,[10] semihomodesmotic,[11] quasihomodesmotic,[12,13] homomolecular homodesmotic,[14] isogeitonic,[15] isoplesitoic,[16] homoplesitoic,[16] and s-homodesmotic[17−19] have since been developed to successfully predict various properties of organic molecules.

Recently, Wheeler, Houk, Schleyer, and Allen offer a detailed account of the widespread inconsistency in the definition of the term "homodesmotic scheme".[20] Recognizing the need for greater uniformity and generality in such reaction schemes, they developed a general and a systematic hybridization-based hierarchy of homodesmotic reactions for closed shell hydrocarbons. By utilizing predefined reactants and products at each level of their hierarchy, they achieve an increased balance in the hybridization and the covalent bonding environment of the carbon atoms within the family of hydrocarbon molecules. They further rightly point out the need for a general and a systematic hierarchy that spans beyond hydrocarbons and is applicable to any organic molecule containing any heteroatom (for instance, O, N, S, etc.). Finally, acknowledging the enormous variety of functional groups that can exist in organic molecules, they clearly indicate that predefining reactants and products for various levels of a hierarchy involving organic molecules is a prominent challenge. Thus the construction of a generalized hierarchy for all closed shell organic molecules has remained an open problem.[4−9,20]

An alternate approach to the construction of the generalized hierarchy, i.e., one based on merely the connectivity of the atoms in an organic molecule instead of utilizing predefined reactants and products in a hybridization-based hierarchy, helps in overcoming this challenge and solves this long-standing problem. Such a hierarchy is applicable to all classes of closed shell organic molecules and does not require significant effort to balance the various coefficients in the chemical equations employed in the hierarchy. Another advantage of such a connectivity-based approach is that it enormously minimizes the use of complicated terminology that is sometimes used in the definition of the different homodesmotic schemes, without any compromise in the goal of preserving the bond types and the hybridization of the atoms involved.

In this work, we develop the general and systematic connectivity-based hierarchy (CBH) for closed shell organic molecules containing various hetero atoms (e.g., N, O, F, P, S, Cl, Br), a variety of functional groups (e.g., alcohols, amines, ketones, aldehydes,

(a)

(b)
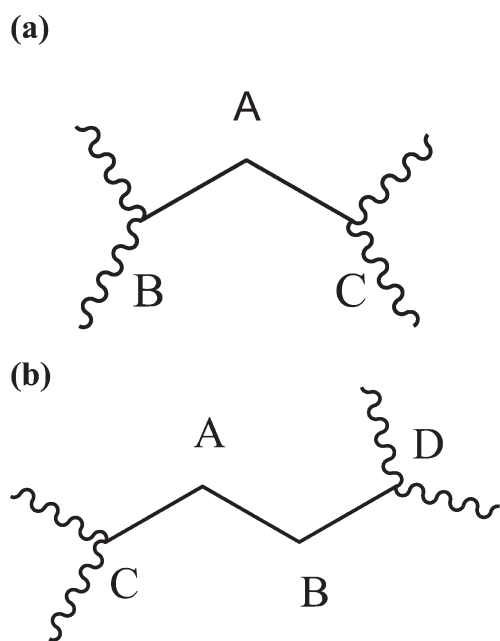
Figure 1. (a) A generic representation of the preservation of atom connectivity. Atom A's connectivity is preserved by keeping it connected with atoms B and C. The wiggly lines merely indicate the extension of the molecule. (b) A generic representation of the preservation of bond connectivity. Bond A—B's connectivity is preserved by maintaining the C—A—B—D framework. The wiggly lines merely indicate the extension of the molecule.

acids, thiols), and different molecular architectures (e.g., acyclic, cyclic, branched, linear) to show how the reaction energy converges better at each increased level in the hierarchy. Construction of the hierarchy requires a knowledge of only the connectivity and the types of bonds (single, double, triple) in the molecule, i.e., *the chemical structure is all that is necessary,* and the reaction schemes can be generated in a simple and automated manner with increasing levels of sophistication. We further go on to prove how the CBH scheme satisfies the bond type and the hybridization requirements set by Wheeler, Houk, Schleyer, and Allen in their hierarchy. Finally, we apply CBH to compute the enthalpies of formation of various closed shell organic compounds and demonstrate how the higher levels of the hierarchy help achieve accurate results using commonly used density functionals with modest double- or triple-ζ quality basis sets.

2. CONSTRUCTION OF THE GENERALIZED CBH FOR ORGANIC MOLECULES

CBH features several rungs at increasing levels of sophistication. They are all based on the local structure and bonding in the molecule under consideration. The rungs alternate between atom- and bond-centric perspectives. The simplest, atom-centric rung is the isogyric scheme[2,4,20] where each heavy (non-hydrogen) atom is extracted in its saturated valence state (e.g., each C as CH_4) by adding appropriate number of hydrogen molecules. The number of hydrogen molecules equals the number of covalent bonds between heavy atoms (counting a double bond as two covalent bonds, etc.). This rung is named CBH-0. The next, bond-centric rung (CBH-1) of the hierarchy is obtained simply by extracting all the heavy-atom bonds in the molecule as isolated valence-satisfied molecules (e.g., a carbon—carbon double bond

as H_2C=CH_2). This is identical to the widely used Pople's isodesmic bond separation scheme.[4] At CBH-2, we preserve the immediate connectivity of all the atoms in the molecule, i.e., every heavy atom is extracted with its immediate bonding environment (Figure 1a). Later, we will show that this is equivalent to the simplest hypohomodesmotic reaction scheme developed by Wheeler et al.[20] Perhaps a more appropriate, simpler, and illuminative name is "isoatomic" scheme (vide infra). Finally, at CBH-3, we preserve the immediate connectivity of all the bonds in the molecule, i.e., every heavy-atom bond is extracted maintaining its immediate connectivity (Figure 1b). Later, we will show that this is equivalent to the simplest hyperhomodesmotic reaction scheme. Higher levels can be defined in a similar manner. For example, at CBH-4, we extract every heavy atom while maintaining two immediate bonds. While additional higher levels can be defined easily, in this paper, we restrict our discussion to the rungs most likely to be useful, viz. CBH-1 to CBH-3.

In each rung, in order to avoid overcounting of the atoms and bonds, additional molecules have to be included as reactants to balance the equations. We show in this paper (vide infra) that this can be accomplished in an elegant and automated manner. This results from the connections between the products formed in one rung and the reactants in the next higher rung of the hierarchy (Figure 2). We illustrate the construction of CBH using a simple example involving a single-ring system without any substituents, cyclopentadiene[21] (C_5H_6, Figure 3a):
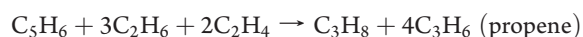
- CBH-0: based on the isogyric scheme.

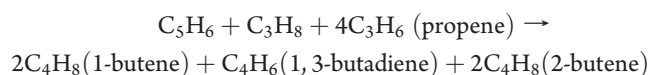$$C_5H_6 + 7H_2 \rightarrow 5CH_4$$

- CBH-1: based on the isodesmic bond separation scheme.

$$C_5H_6 + 5CH_4 \rightarrow 3C_2H_6 + 2C_2H_4$$
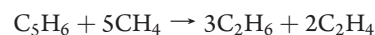
- CBH-2: based on preserving the environment of the atoms (vide infra for more details).

$$C_5H_6 + 3C_2H_6 + 2C_2H_4 \rightarrow C_3H_8 + 4C_3H_6 \text{ (propene)}$$

- CBH-3: based on preserving the environment of the bonds (vide infra for more details).

$$C_5H_6 + C_3H_8 + 4C_3H_6 \text{ (propene)} \rightarrow$$
$$2C_4H_8(1\text{-butene}) + C_4H_6(1,3\text{-butadiene}) + 2C_4H_8(2\text{-butene})$$

The first observation for this simple system is that the products formed in the lower hierarchy appear exactly as the reactants in the next hierarchy along with the parent molecule itself (Figure 2). This is entirely understandable since we are progressively making a larger part of the local bonding environment on both sides of the reaction as similar as possible. For example, each pair of adjacent heavy-atom bonds (products in CBH-1) shares a common heavy atom (as reactants in CBH-1 as well as products in CBH-0). Similarly, each pair of adjacent atoms preserving their immediate environment (products in CBH-2) shares a common heavy-atom bond (reactants in CBH-2 as well as products in CBH-1). Clearly, the additional reactants at each level are necessary to take care of the double counting that would otherwise be present. Since the products in any hierarchy are easily derived from the local bonding environment as noted earlier, the procedure can be easily automated giving considerable advantage to our scheme. For example,
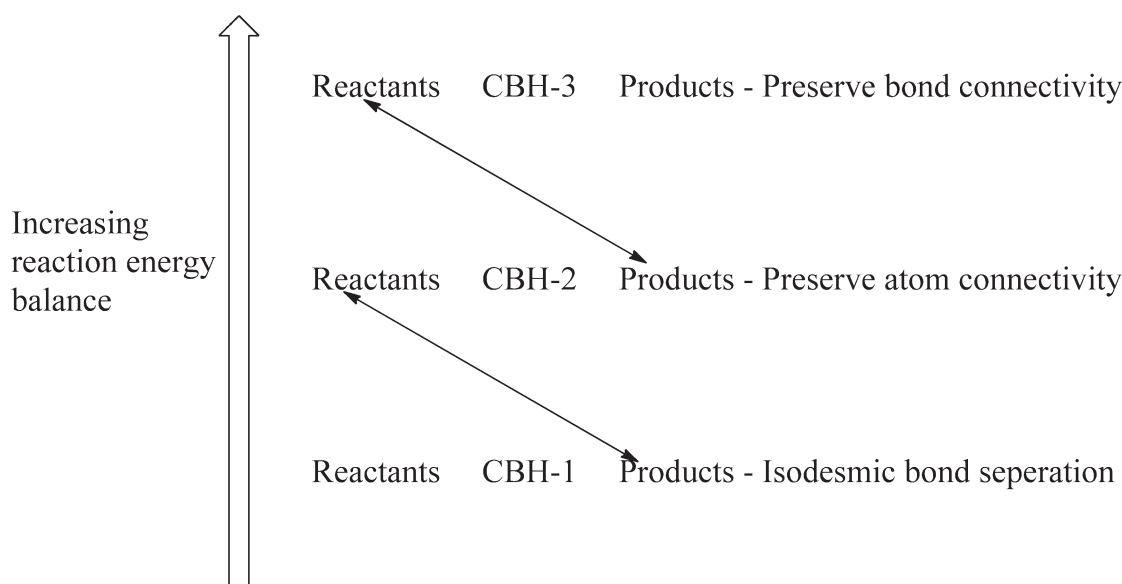
Figure 2. Showing the connection between various rungs of CBH. Reactants and products at the first rung (CBH-1) are obtained based on Pople's IBS scheme. Products of CBH-1 then become the reactants for the next rung (CBH-2). The products for CBH-2 are obtained by preserving the atom connectivity as shown in Figure 1a. Reactants for the third rung (CBH-3) are in turn the same as the products for CBH-2. Products for CBH-3 are then obtained by preserving the bond connectivity as shown in Figure 1b.
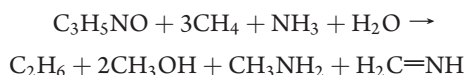
the CBH schemes can be written for other hydrocarbon ring systems, such as 1,3-cyclohexadiene, cyclohexane, etc.

The scheme can also be easily extended to molecules containing heteroatoms. For example, if we take oxazoline (Figure 3b), a simple heterocyclic ring containing oxygen and nitrogen where every heavy atom has a different bonding environment, we have the following reactions:
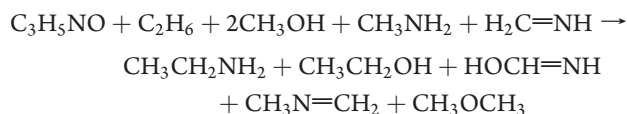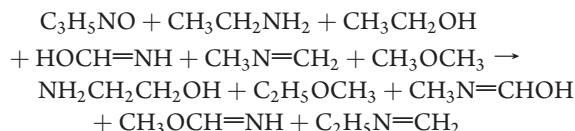
- CBH-0: based on the isogyric scheme.

$$C_3H_5NO + 6H_2 \rightarrow 3CH_4 + NH_3 + H_2O$$
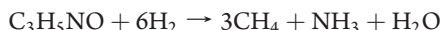
- CBH-1: based on the IBS scheme.

$$C_3H_5NO + 3CH_4 + NH_3 + H_2O \rightarrow$$
$$C_2H_6 + 2CH_3OH + CH_3NH_2 + H_2C=NH$$

- CBH-2: based on preserving the environment of the atoms

$$C_3H_5NO + C_2H_6 + 2CH_3OH + CH_3NH_2 + H_2C=NH \rightarrow$$
$$CH_3CH_2NH_2 + CH_3CH_2OH + HOCH=NH$$
$$+ CH_3N=CH_2 + CH_3OCH_3$$

- CBH-3: based on preserving the environment of the bonds

$$C_3H_5NO + CH_3CH_2NH_2 + CH_3CH_2OH$$
$$+ HOCH=NH + CH_3N=CH_2 + CH_3OCH_3 \rightarrow$$
$$NH_2CH_2CH_2OH + C_2H_5OCH_3 + CH_3N=CHOH$$
$$+ CH_3OCH=NH + C_2H_5N=CH_2$$

Again, the products in one hierarchy become the reactants in the next hierarchy, and the products of the balanced reaction can be written by inspection or by an automated program. It is worthwhile to observe here that, even for a simple molecule like oxazoline, using a reaction scheme involving predefined reactants and products may introduce complications in selecting and balancing uniquely defined equations at the higher rungs of the hierarchy.

Thus far we have considered simple cyclic systems without any branching or side groups. In order for us to construct the CBH for any organic molecule, cyclic/acyclic and with/without a branching group as well, we need to understand two additional simple facets. Both are straightforward to implement and can also be automated easily.

3. CANCELLATION OF THE MOLECULES REPRESENTING THE TERMINAL MOIETIES

The first new facet that we consider involves molecules that have terminal moieties. For example, in an *n*-alkane chain, the two methyl groups at the two ends are terminal moieties. It is clear that such groups are different from the units in a simple cyclic system considered earlier. The principal difference is that such a terminal moiety does not have two (or more) heavy-atom bonds. In such cases, it is easy to see that (vide infra) the molecules representing such terminal moieties need to be treated differently and get canceled as reactants in the equations representing the next hierarchy.

Further, it is readily seen at different rungs of the hierarchy that we have different molecules representing the terminal moieties. For example, in *n*-heptanethiol (vide infra for the construction of the CBH), the terminal moieties are the methyl and the thiol groups. The molecules representing these moieties as reactants in the different hierarchies are: methane and hydrogen sulfide at CBH-1, ethane and methanethiol at CBH-2, etc.

The cancellation of the molecules that represent terminal moieties can be seen using an example involving an open chain molecule without branching, *n*-heptanethiol ($C_7H_{16}S$, Figure 3c):

CBH-0: isogyric

$$C_7H_{16}S + 7H_2 \rightarrow 7CH_4 + H_2S$$
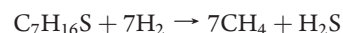
It is clear that the molecules representing the terminal moieties (one molecule of methane and a molecule of hydrogen sulfide) do not appear as reactants at the next level. The CBH-1 scheme is, thus:

(a)

(b)

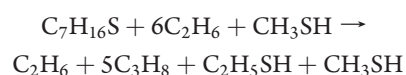
(c)

(d)

(e)
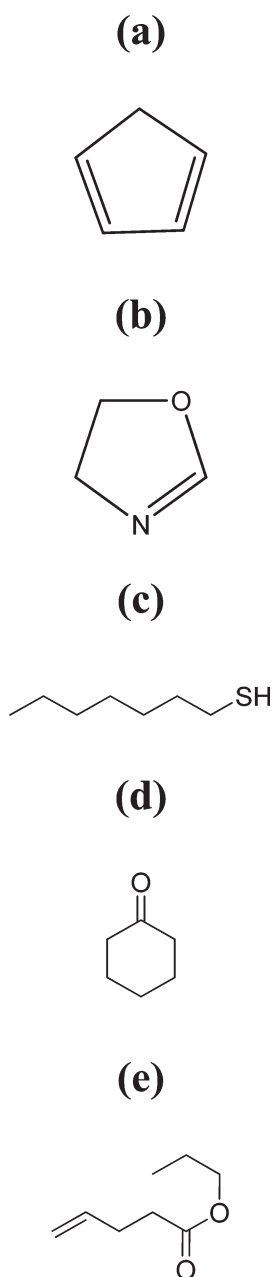
Figure 3. Various molecules used as examples to illustrate CBH: (a) cyclopentadiene, (b) *n*-heptane thiol, (c) oxazoline, (d) cyclohexanone and (e) propyl-pent-4-enoate.

CBH-1: after terminal moiety cancellation

$$C_7H_{16}S + 6CH_4 \rightarrow 6C_2H_6 + CH_3SH$$

The reaction representing the next hierarchy is:
 CBH-2: preserving the environment of the atoms

$$C_7H_{16}S + 6C_2H_6 + CH_3SH \rightarrow$$
$$C_2H_6 + 5C_3H_8 + C_2H_5SH + CH_3SH$$

Here, the products that maintain the local environments of each of the heavy atoms, share some common species with the reactants. After cancellation of common species, we get

$$C_7H_{16}S + 5C_2H_6 \rightarrow 5C_3H_8 + C_2H_5SH$$

(a)

(b)
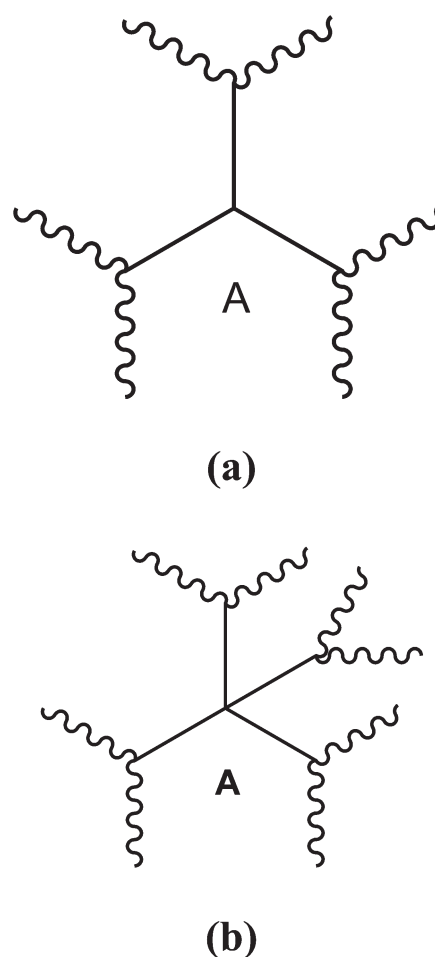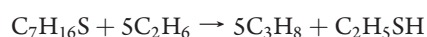
Figure 4. (a) A generic representation of a branch point. Here the branching point is the atom A. The molecule representing this branch point as a reactant is counted twice at the bond-centric rungs. (b) A generic representation of two branch points on the same atom.

Again, the molecules representing the terminal moieties (one molecule of ethane and a molecule of methanethiol) get canceled in this hierarchy.

Using the same logic, one molecule of propane and a molecule of ethanethiol gets canceled in the next hierarchy, and we get
 CBH-3: after cancellation

$$C_7H_{16}S + 4C_3H_8 \rightarrow 4C_4H_{10} \text{ (}n\text{-butane)} + C_3H_7SH \text{ (}n\text{-propanethiol)}$$

Overall, the molecules representing the terminal moieties (which are products at a lower rung) do not appear in the next hierarchy.

4. TAKING BRANCHING INTO ACCOUNT: A MOLECULE REPRESENTING A BRANCH POINT IS COUNTED TWICE PER BRANCH

Given the enormous affinity of carbon toward catenation, branching of certain bonds in the structural framework of an organic molecule is very common. At any branching point in an organic molecule, the atom at the branching point is attached to one additional heavy atom in comparison to an atom not at the branching point, i.e., there is an additional covalent bond that needs to be considered at the branching

points. These can be taken into account by adjusting the coefficients of the defining molecules that represent the branch points. These molecules are counted twice per branch when they occur as reactants (Figure 4a). Similarly, if there is an additional branch (Figure 4b, e.g., the central carbon in neopentane), then the molecule as a reactant has to be counted thrice overall.

Such a coefficient takes into account the overcounting that would otherwise occur in a simplistic pairwise treatment of intersecting bonds.[22] It is important to note here that branching occurs only with bonds. This is due to the fact that, while an atom can be at the intersection of multiple bonds, each covalent bond terminates at exactly two atoms. Thus, the phenomenon of counting twice is applicable only at the bond centric-rungs, i.e, at CBH-1 and CBH-3.

We illustrate this facet of CBH using cyclohexanone ($C_6H_{10}O$, Figure 3d) as an example. Here, the branching point occurs at the carbonyl carbon. The molecule representing this branching point at CBH-1 is methane. Therefore, methane needs to be counted twice in CBH-1. Similarly, the molecule representing the branch point at CBH-3 is acetone and hence is counted twice at that rung.
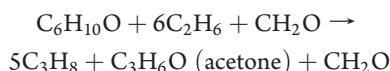
CBH-0:

$$C_6H_{10}O + 8H_2 \rightarrow 6CH_4 + H_2O$$
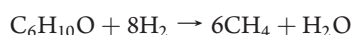
CBH-1: a combination of terminal moiety cancellation and taking the branch point into account

$$C_6H_{10}O + 7CH_4 \rightarrow 6C_2H_6 + CH_2O \text{ (formaldehyde)}$$
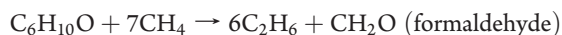
Due to the terminal moiety cancellation, water does not appear in the reactants. On the other hand, due to methane representing a branching point, it is counted twice.
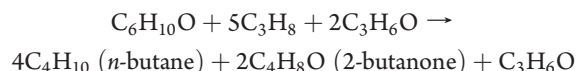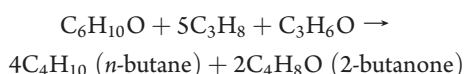
CBH-2:

$$C_6H_{10}O + 6C_2H_6 + CH_2O \rightarrow$$
$$5C_3H_8 + C_3H_6O \text{ (acetone)} + CH_2O$$

i.e.,

$$C_6H_{10}O + 6C_2H_6 \rightarrow 5C_3H_8 + C_3H_6O \text{ (acetone)}$$

CBH-3: counting acetone twice

$$C_6H_{10}O + 5C_3H_8 + 2C_3H_6O \rightarrow$$
$$4C_4H_{10} \text{ (}n\text{-butane)} + 2C_4H_8O \text{ (2-butanone)} + C_3H_6O$$

i.e.,

$$C_6H_{10}O + 5C_3H_8 + C_3H_6O \rightarrow$$
$$4C_4H_{10} \text{ (}n\text{-butane)} + 2C_4H_8O \text{ (2-butanone)}$$

The same procedure is thus adopted for any molecule possessing a branched molecular architecture. The Supporting Information features another example of the construction of CBH for a more complex branched molecule.

5. STRAIGHTFORWARD BALANCING OF THE CHEMICAL EQUATIONS AND AUTOMATED

CBH starts with the simple isogyric scheme at the lowest rung (CBH-0). It preserves the atom and bond connectivities such that products of a lower rung occur as the reactants at higher rungs—with two minor modifications: First, the terminal moieties get canceled out. At bond-centric rungs (CBH-1 and CBH-3), molecules representing a branch

position are counted twice per branch. Since these are the only features of CBH, balancing of the chemical equations involved in the hierarchy naturally follows the construction of the hierarchy. Further, since the CBH is entirely automated, given any molecule, the reaction schemes are generated with ease.

6. GENERAL AND UNIQUE FOR ANY CLOSED SHELL ORGANIC MOLECULE AND AVOIDS COMPLICATED TERMINOLOGY

Our hierarchy is based on the connectivity of the atoms in an organic molecule. Hence, it is independent of the elements present in the organic molecule. This makes it general for all organic molecules. Since the connectivity of the atoms in a molecule is fixed, there is only one way of constructing the hierarchy. Thus, CBH is unique for any organic molecule. CBH therefore does not offer the scope for definition-based inconsistencies noted by Wheeler, Houk, Schleyer, and Allen in the homodesmotic schemes (vide supra).

Moreover, the hierarchy does not involve any complicated terminology. The only terms used in the hierarchy are: (a) CBH, connectivity-based hierarchy; (b) molecule representing a terminal moiety; and (c) molecule representing the branch point.

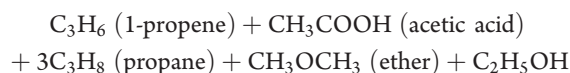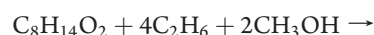## 7. HOW DOES CBH PRESERVE HYBRIDIZATION AND BOND TYPES?

In this section, we show how CBH, in addition to being general and unique for all closed shell organic molecules, preserves the hybridization and the bond types as prescribed by Wheeler, Houk, Schleyer, and Allen in their homodesmotic hierarchy for hydrocarbons as well. Propyl-pent-4-enoate ($C_8H_{14}O_2$, Figure 3e), having both carbon atoms as well as heteroatoms in different states of hybridizations, is chosen as an example to demonstrate the preservation of hybridization and the bond types. Since CBH-0 corresponds to the trivial, isogyric scheme, which is known to have considerable imbalances in the reaction energies,[4−6,20] we henceforth start only from the CBH-1 rung.

CBH-1:

$$C_8H_{14}O_2 + H_2O + 7CH_4 \rightarrow 5C_2H_6 + C_2H_4 + H_2CO + 2CH_3OH$$

This rung of CBH, utilizing Pople's IBS scheme, corresponds to the RC2 level of the homodesmotic hierarchy for closed shell hydrocarbons developed by Wheeler, Houk, Schleyer, and Allen.

CBH-2:

$$C_8H_{14}O_2 + 4C_2H_6 + 2CH_3OH \rightarrow$$
$$C_3H_6 \text{ (1-propene)} + CH_3COOH \text{ (acetic acid)}$$
$$+ 3C_3H_8 \text{ (propane)} + CH_3OCH_3 \text{ (ether)} + C_2H_5OH$$

This rung maintains the numbers of all heavy atoms in their different states of hybridization as well as the numbers of all heavy atoms (regardless of the hybridization state) attached to the appropriate number of hydrogens (0−3). Thus, the CBH-2 rung corresponds to the RC3 (hypohomodesmotic) level of the n-homodesmotic hierarchy for closed shell hydrocarbons. Due to the confusion in the existing literature on the names of thermochemical schemes, we would like to suggest a more appropriate, much simpler and illuminative name "isoatomic" scheme for this useful rung, since it
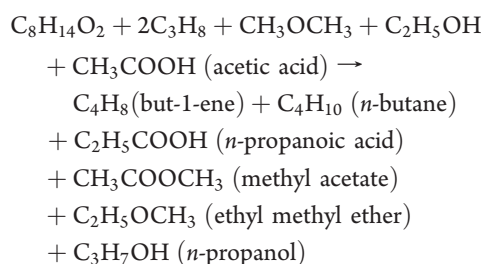
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Table 1. Zero Point and Thermal Corrected Mean Absolute Reaction Energies (kcal/mol) Computed Using CBH[a,b]

density functional	CBH-1	CBH-2	CBH-3
BPW91	26.51	1.38	0.93
BMK	28.79	1.13	0.52
B3LYP	26.15	1.30	0.65
M05-2X	31.71	1.15	0.59
M06-2X	31.00	1.53	0.70
TPSSh	25.88	1.08	0.62
B2PLYP	29.52	0.95	0.51

[a] All the geometries were optimized at the B3LYP/6-31G(2df,p) level. A scale factor of 0.9854 was applied to the harmonic frequencies obtained. [b] 6-311++G(3df,2p) basis set was used throughout.

preserves the immediate environment of all the heavy atoms in an organic molecule.

CBH-3:

$$C_8H_{14}O_2 + 2C_3H_8 + CH_3OCH_3 + C_2H_5OH$$
$$+ CH_3COOH \text{ (acetic acid)} \rightarrow$$
$$C_4H_8 \text{(but-1-ene)} + C_4H_{10} \text{ (}n\text{-butane)}$$
$$+ C_2H_5COOH \text{ (}n\text{-propanoic acid)}$$
$$+ CH_3COOCH_3 \text{ (methyl acetate)}$$
$$+ C_2H_5OCH_3 \text{ (ethyl methyl ether)}$$
$$+ C_3H_7OH \text{ (}n\text{-propanol)}$$

CBH-3 maintains the number of bond types for all heavy-atom bonds (e.g., H_3C-O, H_2C-O, $HC-O$, $C-O$, etc.) as well as the numbers of each type of heavy atoms in the same hybridization state (sp^3, sp^2, sp) attached to appropriate number of hydrogens (0−3). This is as prescribed at the RC5 (hyperhomodesmotic) level of the homodesmotic hierarchy for closed shell hydrocarbons.

The same logic can be extended to all the closed shell organic molecules, and it can be easily shown that CBH preserves the appropriate hybridizations as well as the bond types. It is important to note here that, throughout the construction of the hierarchy, we present a general, physical picture of an organic molecule, solely based on the connectivity of the atoms in the molecule. Terms such as hybridization and bond multiplicities are never used herein. Yet, the hierarchy preserves (vide supra) both the bond multiplicities as well as hybridization.

8. WHAT IS THE REASON FOR THE WIDESPREAD DEFINITION-BASED INCONSISTENCY?

Since our physically motivated, chemical structure-based method does not correspond with the homodesmotic scheme but instead maps appropriately with the hypohomodesmotic and hyperhomodesmotic schemes developed by Wheeler et al.,[20] this work enables us to point out that, in general, for any closed shell organic molecule, *the homodesmotic scheme does not have a fundamental structure-based origin.* This is the principal reason for the widespread definition-based inconsistencies noted in the homodesmotic scheme. Wheeler and co-workers had previously noted that multiple definitions of "homodesmotic reactions" are available for the family of closed shell hydrocarbons but simply observed that "homodesmotic reactions must be considered a special case."[20]

A final important point to note is that many different hypo- and hyperhomodesmotic schemes can be written for a given molecule. However, by merely examining the chemical structure

Table 2. Computed Reaction Energies using CBH[a]

molecular formula	chemical name	CBH-1	CBH-2	CBH-3
$C_4H_{10}N_2$	piperazine	21.77	4.22	−3.16
$C_5H_{10}O$	3-pentanone	26.95	0.64	−0.04
$C_5H_{10}O_2$	isopropyl acetate	59.68	−1.76	0.57
$C_5H_{12}S$	ethyl propyl sulfide	10.76	−0.26	0.07
$C_6H_{13}NO_2$	6-aminohexanoic acid	57.48	−1.27	−0.10
$C_6H_{12}O$	cyclohexanol	23.13	−1.43	−1.53
$C_6H_{10}O$	cyclohexanone	30.77	−3.15	−3.67
$C_6H_{12}S$	cyclohexanethiol	19.05	−1.40	−0.62
$C_6H_{11}Cl$	cyclohexyl chloride	21.88	−1.26	−1.58
$C_6H_{13}Br$	n-hexyl bromide	14.01	−0.28	−0.14
$C_7H_{12}O$	cyclohexanal	28.18	−2.61	−0.92
$C_7H_{16}S$	1-heptanethiol	15.18	−0.27	0.06
$C_8H_{15}N$	octanenitrile	26.63	−0.78	0.11
$C_8H_{19}N$	dibutylamine	22.17	−0.97	−0.53
$C_8H_{14}O_2$	propyl pent-4-enoate	65.94	−2.25	0.19
$C_8H_{16}O$	t-butyl isopropyl ketone	37.06	−2.99	0.04
$C_{10}H_{18}$	2-decyne	30.40	−2.56	−0.08
$C_{10}H_{19}N$	caprinitrile	31.58	−0.90	0.06
$C_{11}H_{21}N$	1-cyanodecane	33.92	−1.10	−0.10
$C_{12}H_{24}O$	decyl methyl ketone	43.53	−0.53	−0.57

[a] At the M06−2X/6-311++G(3df,2p) // B3LYP/6-31G(2df,p) level of theory. The reaction energies include zero-point and thermal corrections (see text).

of any organic molecule, the simplest and unique reaction schemes are the ones generated using our CBH-2 and CBH-3 rungs. Overall, the n-homodesmotic reaction scheme for closed shell hydrocarbons indicated by Wheeler et al.[20] is similar in spirit to our hierarchy. However, our structure-based formalism is much more general, applicable to a substantially wider variety of molecules and avoids any definition-based inconsistencies noted previously in the homodesmotic hierarchy. Further, it is easily constructed without using predefined reactants and products, resulting in substantial simplicity in the implementation.[21]

9. TEST SET

In our efforts to duly represent the enormous structural variety of organic compounds, we have chosen organic molecules containing the following features: a variety of functional groups (for instance, alcohols, amines, ketones, aldehydes, acids, thiols), hetero atoms (N, O, F, S, Cl, Br), and different molecular architectures (for instance, acyclic, cyclic, branched, linear). Our test set consists of 20 molecules containing between 6 and 12 heavy atoms, consistent with our goal of applying these methods to larger and more general classes of organic molecules. The complete test set is provided in the Supporting Information as well as in Table 2 (vide infra).

10. COMPUTATIONAL METHODS

All the computations have been performed using the Gaussian 09[23] suite of programs. In this initial evaluation study, we have used seven different density functional methods, possessing different rungs of exchange and correlation energy functionals. They are: (a) the BPW91 generalized gradient approximation (GGA) functional,[24−26] (b) the kinetic energy density (τ) dependent BMK functional,[27] (c) the popular B3LYP[28,29] hybrid

functional, (d and e) Truhlar's meta-exchange—correlation functionals, M05-2X[30] and M06-2X,[31] (f) Perdew and Scuseria's hybrid meta-GGA functional TPSSh,[32] and (g) Grimme's double-hybrid functional B2PLYP.[33]

To obtain reliable geometries, we use the same level of theory as employed by the popular G4 method,[34,35] i.e., B3LYP/6-31G-(2df,p) level. A scale factor of 0.9854 was applied in the calculation of the zero point and thermal corrections to the enthalpy. The optimized geometries were then used in single point calculations using the six different density functionals (vide supra). Six different modest-sized basis sets, three with Pople-style (6-31+G(d,p), 6-31G(2df,p), and 6-311++G(3df,2p)) and three with Dunning-style (aug-cc-pVDZ, cc-pVTZ, and aug-cc-pVTZ) have been used in these single point computations to study the effect of the basis sets. While much larger basis sets are needed to get converged results, we use these more practical, modest basis sets to evaluate if they are sufficient to have significant error cancellations. As expected from the systematic construction of the CBH,

we do indeed observe that they lead to considerable cancellation (vide infra).

11. RESULTS AND DISCUSSION

We evaluate the performance of CBH in two steps: In the first step, we evaluate the reaction energies for a test set of molecules at the different rungs of the hierarchy. Since there is an increasingly better matching of the bond types, the reaction energies should get smaller at the higher hierarchies. This is similar to the approach used by Wheeler et al. In the second step, we apply the CBH to evaluate the enthalpies of formation for the set of molecules at different hierarchies and compare to the available experimental data.

A. Performance of CBH: Reaction Energy Convergence Table 1 provides the mean absolute values for the reaction energies computed at the different rungs of CBH. It can be readily seen that, for all the density functionals, as we go from CBH-1 to CBH-3, there is a greater balance of the bond types leading to a decrease in the calculated reaction energies. At CBH-1, the mean absolute value of the reaction energies varies from 25 to 31 kcal/mol (Table 1). It is consistently observed that, both at CBH-2 and CBH-3, the mean absolute reaction energies are less than 2 kcal/mol. In fact, the numbers obtained at CBH-3 level indicate convergence to the subkcal/mol level. These results suggest that chemical accuracy (typically taken to be $\pm 1-2$ kcal/mol) may be possible even with such simple theoretical models.

A glance at Table 2 reveals the performance of the individual molecules at the three rungs (data for the M06-2X functional are given in Table 2, and data for the rest of the functionals are given in the Supporting Information). For all the molecules, irrespective of the functional used, reaction energies at CBH-1 are found to be endothermic. At CBH-2 and CBH-3, significant improvement is seen: the smaller reaction energies indicating better

Table 3. Zero Point and Thermal Corrected Mean Absolute Reaction Energies (kcal/mol) for Different Pople and Dunning Style double- and triple-ζ Basis Sets^{a,b}

basis set	CBH-1	CBH-2	CBH-3
6-31+G(d,p)	30.76	1.66	0.79
6-31 g(2df,p)	30.41	1.20	0.91
6-311++g(3df,2p)	31.00	1.53	0.70
aug-cc-pVDZ	29.67	1.88	0.79
cc-pVTZ	29.93	1.40	0.76
aug-cc-pVTZ	30.02	1.42	0.72

^{a} All the geometries were optimized at the B3LYP/6-31G(2df,p) level. A scale factor of 0.9854 was applied to derive the zero point and thermal energies. ^{b} The M06—2X density functional was used throughout.

Table 4. Difference between Experimentally Determined Enthalpies of Formations and Computed Enthalpies of Formation (298 K, expt—theory, kcal/mol) at the Various Rungs of CBH {M06-2X/6-311++G(3df,2p)//B3LYP/6-31G(2df,p)}

molecular formula	chemical name	expt ΔH_f	$\pm$	CBH-1	CBH-2	CBH-3
$C_4H_{10}N_2$	piperazine	6.0^a	1.5	−3.61	−6.38	0.98
$C_5H_{10}O$	3-pentanone	−61.7^b	0.2	0.04	1.12	0.33
$C_5H_{10}O_2$	isopropyl acetate	−115.1^b	0.1	−2.62	−0.66	0.11
$C_5H_{12}S$	ethyl propyl sulfide	−25.03^a	0.19	−1.71	−0.28	0.28
$C_6H_{13}NO_2$	6-aminohexanoic acid	−115.28^a	0.72	−3.24	−2.25	0.29
$C_6H_{12}O$	cyclohexanol	−69.3^b	0.2	−2.99	−1.02	−0.93
$C_6H_{10}O$	cyclohexanone	−55.23^a	0.21	−3.32	−1.96	−1.61
$C_6H_{12}S$	cyclohexanethiol	−22.88^a	0.19	−3.19	−1.38	−0.95
$C_6H_{11}Cl$	cyclohexyl chloride	−39.79^a	0.46	−3.14	−2.53	−0.72
$C_6H_{13}Br$	n-hexyl bromide	−35.88^a	0.49	−2.77	−1.28	−1.21
$C_7H_{12}O$	cyclohexanal	−56.2^b	NA	−4.70	−2.57	−1.29
$C_7H_{16}S$	1-heptanethiol	−35.73^a	0.23	−2.01	−0.37	0.72
$C_8H_{15}N$	octanenitrile	−12.1^a	0.36	−1.72	−1.06	0.71
$C_8H_{19}N$	dibutylamine	−40.89^a	0.76	−5.61	−6.18	−2.88
$C_8H_{14}O_2$	propyl pent-4-enoate	−95.1^a	0.8	−2.40	0.05	1.84
$C_8H_{16}O$	t-butyl isopropyl ketone	−80.86^a	0.29	−2.58	0.19	−0.55
$C_{10}H_{18}$	2-decyne	5.63^a	0.82	−0.73	−1.61	0.47
$C_{10}H_{19}N$	caprinitrile	−21.9^a	0.43	−2.20	−1.14	0.86
$C_{11}H_{21}N$	1-cyanodecane	−27.10^a	0.48	−2.88	−1.62	0.50
$C_{12}H_{24}O$	decyl methyl ketone	−96.62^a	0.59	−3.15	−0.97	−0.09

^{a} Experimental enthalpies of formation taken from the NIST Web site. ^{b} Experimental enthalpies of formation taken from ref 36.

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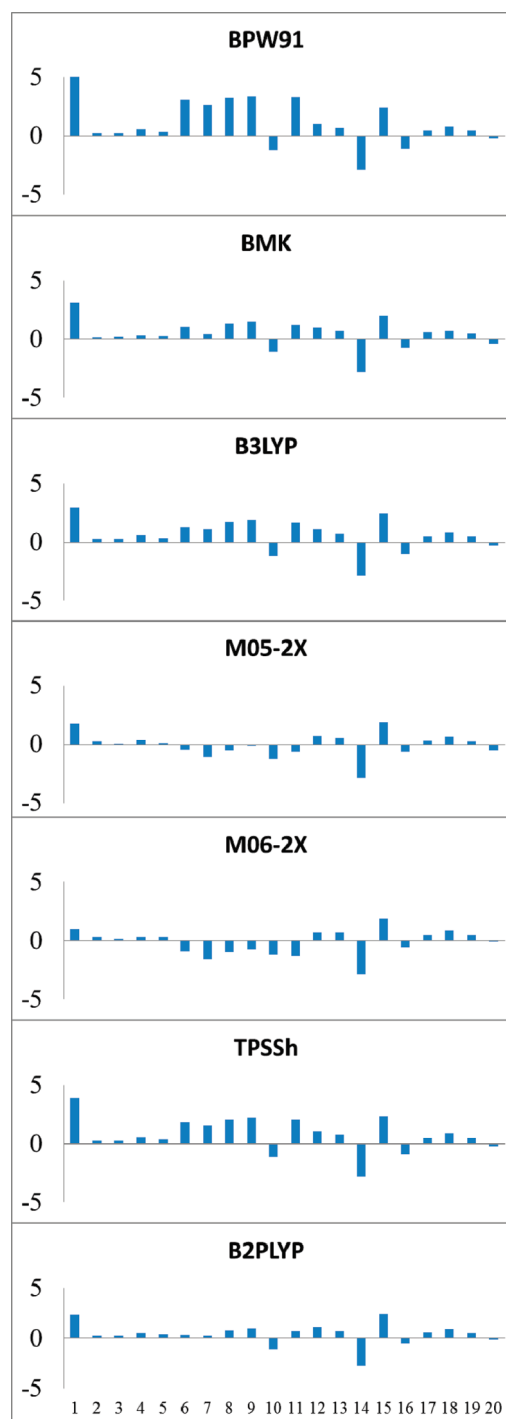dx.doi.org/10.1021/ct200279q |J. Chem. Theory Comput. 2011, 7, 2094–2103
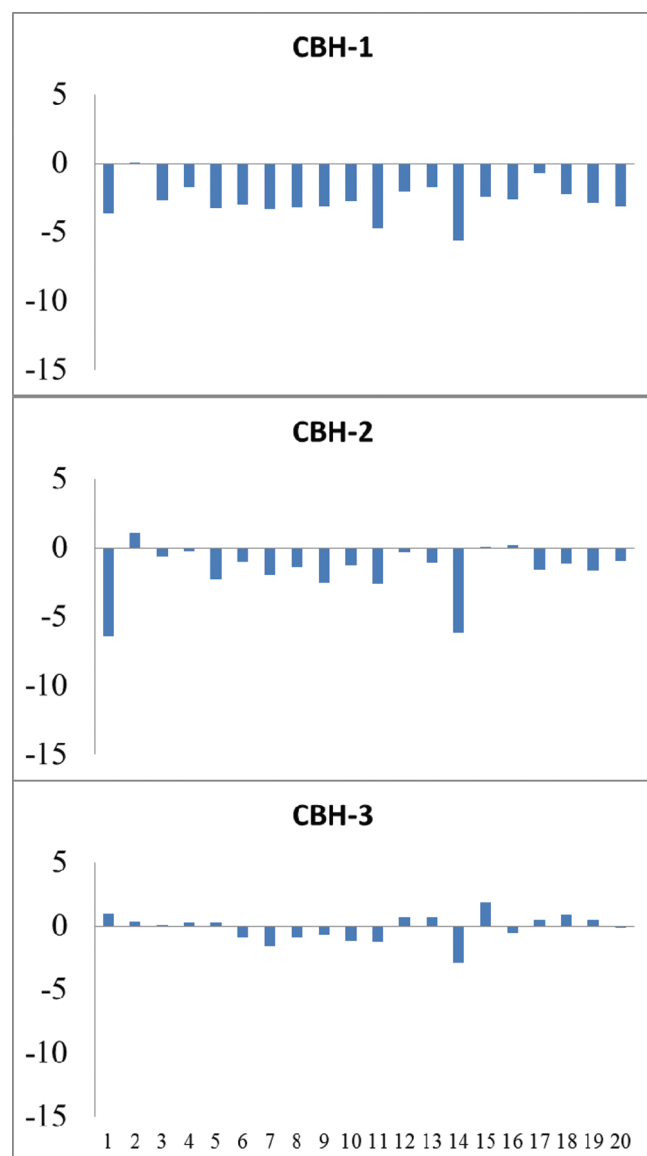
Figure 5. Pictorially depicting the errors (experiment−theory, vertical axis, kcal/mol; also see Table 4) for all the molecules used in the test set. The molecules listed in the horizontal axis follow the same order as listed in Table 4. Data are provided here at the M06-2X/6-311++G(3df,2p) // B3LYP/6-31G(2df,p) level of theory. Supporting Information provides the data for rest of the density functionals used.

Figure 6. A comparison of the errors (experiment−theory, vertical axis, kcal/mol) in the enthalpies of formation of all the molecules used in our test set at the CBH-3 rung using different density functionals. The molecules listed in the horizontal axis follow the same order as listed in Table 4 (and Tables S8−S13 in the Supporting Information).

balance for the various heteroatom substituents as well as for different molecular architectures.

B. Cases When the Reaction Energies Do Not Appropriately Get Balanced. When CBH is constructed for an aromatic molecule, such as azulene, it is clear that the aromaticity is not preserved. This leads to imbalances in the reaction energies at various rungs (see Supporting Information). Similarly, for a strained bicyclic organic compound such as camphor, the extent of the ring strain is not exactly balanced upon the construction of CBH. Thus, the reaction energies do not converge for such strained molecules at the different rungs (see Supporting Information).

A molecule such as hexafluoro-2,4-hexadiyne nicely illustrates the significance of appropriately preserving the electronic

environment in leading to a balance in the reaction energies. For this diyne, (see Supporting Information) at CBH-2 there is a considerable imbalance in the reaction energies. However, at CBH-3 the reaction energy is well balanced. A possible reason might be that, in the construction of CBH-2 for hexafluoro-2,4-hexadiyne, the products side does not involve any molecule which has a fluorine atom as well as a triple bond in the same molecule, i.e., the electronic

environment of hexafluoro-2,4-hexadiyne is not appropriately preserved. At CBH-3, the products side does involve a molecule which has a fluorine atom as well as a triple bond in the same molecule, and hence the reaction energy gets balanced at CBH-3.

C. Effect of the Basis Sets. CBH works robustly with both Pople-style as well as Dunning-style basis sets. Table 3 demonstrates how the mean absolute values for the reaction energies converge better as we move up the hierarchy. CBH performs well for the double-ζ as well as triple-ζ basis sets, once again illustrating the enhanced balancing of reaction energies at the higher rungs of the hierarchy. It is also observed that, for each rung, the mean absolute reaction energies do not oscillate much (Table 3) upon changing the basis sets. At CBH-3, for all the basis sets employed, convergence of the unsigned averages for the reaction energies toward subkcal/mol is noticed as well. Thus, even by merely using double- and triple-ζ basis sets routinely employed by even nonexperts in theory these days, a very high degree of convergence in the reaction energies is noted, thereby illustrating the practical utility of CBH.

D. Performance of CBH: Application to Computing Enthalpies of Formations. Table 4 contains the difference between the experimentally determined enthalpies of formations and the computed enthalpies of formation (at 298 K, kcal/mol) at the various rungs of CBH [M06-2X/6-311++G(3df,2p)// B3LYP/6-31G(2df,p) shown with the results for the rest of the functionals provided in the Supporting Information]. At each rung, the computed reaction energies have been used in conjunction with the experimentally determined enthalpies of formation for all the molecules that appear as reactants and products (at that particular rung). Experimental enthalpies of formation have been obtained from the NIST Web site and reference.[36] Errors in the computed enthalpies of formation for all the molecules are shown pictorially in Figure 5 (as well as in the Supporting Information) for the different rungs of the hierarchy.

For most of the molecules (Table 4, Figure 5, and Supporting Information), the difference between the experimentally observed enthalpies of formations and the corresponding computed values (kcal/mol) decreases dramatically as we go from CBH-1 to CBH-3. For the M06-2X functional (Table 4), the largest error at the CBH-3 level (−2.88 kcal/mol) occurs for dibutylamine. It is interesting to note that a nearly identical error for dibutylamine occurs for all seven density functionals (Table 4, Supporting Information). Figure 6 shows the errors in the computed enthalpies of formation for all the molecules at the CBH-3 rung for each of the seven functionals. There is clearly some correlation in the performance of the different density functionals. This may be useful in the future to separate the contributions of systematic vs random errors in such calculated enthalpies of formation.

Table 5 lists the mean absolute errors in the calculated enthalpies of formation for the 20 molecule test set for the 7 different density functionals used. Substantial improvement is noted on ascending from CBH-1 to CBH-2 in all cases with the best results for the B2PLYP functional. As expected, (based on the smaller changes in reaction energies, Table 1), going up from CBH-2 to CBH-3 leads to a less dramatic improvement. For all except the lowest rung BPW91 functional, some improvement is seen on going from CBH-2 to CBH-3. The most prominent improvement is noted with Truhlar's M05-2X and M06-2X functionals, though Grimme's B2PLYP double hybrid functional also has a mean absolute deviation of less than 1 kcal/mol. The mean absolute deviation from experiment is less than 2 kcal/mol at both CBH-2 and CBH-3 levels for all the density functionals,

Table 5. Mean Absolute Errors in the Calculated Enthalpies of Formation (298 K, kcal/mol) using CBH[a,b]

density functional	CBH-1	CBH-2	CBH-3
BPW91	7.22	1.59	1.68
BMK	4.93	1.29	1.00
B3LYP	7.57	1.56	1.17
M05-2X	2.07	1.37	0.75
M06-2X	2.73	1.73	0.86
TPSSh	7.85	1.30	1.29
B2PLYP	4.21	1.15	0.89

[a] 6-311++G(3df,2p) basis set was used throughout. [b] Experimental enthalpies of formation taken from the NIST Web site or from ref 36 (see Table 4 for more details).

remarkable considering the size of the molecules and the modest levels of theory used (DFT with DZP or TZP basis sets).

Overall, at the higher rungs of the hierarchy, sub kcal/mol accuracy is readily achieved in the enthalpies of formation as well as the reaction energies, thus indicating the widespread utility of CBH.

12. CONCLUSIONS AND SCOPE

In this work, we have developed the connectivity-based hierarchy (CBH), general and unique for all closed shell organic molecules. Construction of the hierarchy is straightforward, and it does not involve any complicated terms. The hierarchy preserves the hybridization and the bond types for all closed shell organic molecules, thus generalizing the homodesmotic hierarchy for closed shell hydrocarbons developed by Wheeler, Houk, Schleyer, and Allen to all closed shell organic molecules.

Generalization of their hierarchy to all organic molecules, constructed utilizing predefined reactants and products, presents the challenge of encompassing the massive structural variety possible with organic molecules. By employing a physical picture based merely on the atom connectivity in an organic molecule, we are able to generalize our CBH to all closed shell organic molecules, thus solving a long-standing problem in theoretical thermochemistry. Ascending up the rungs of CBH offers a greater reaction balance. We have demonstrated using different density functionals here, that, with merely using double- or triple-ζ basis sets, satisfactory reaction energy balance can be obtained. The success of CBH, however, depends on how well the environment of a molecule is preserved. Thus in certain cases, such as in aromatic molecules and strained molecules, when the aromaticity or the ring strain is not appropriately preserved, the reaction energies do not get balanced, even at higher rungs of the hierarchy.

Application of CBH to compute enthalpies of formations of various organic molecules shows that the computed values agree well with respect to experimentally observed values. We are currently working on theoretical predictions of thermochemical properties of a variety of organic molecules using CBH with density functional theory as well as wave function-based methods.

■ ASSOCIATED CONTENT

⑤ Supporting Information. The performance of all the molecules in the test set using different functionals are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) In the Supporting Information of ref 20, the authors construct their *n*-homodesmotic schemes for cyclopentadiene and 1,3-cyclohexadiene. Inspection of their scheme for the RC5 level in their hierarchy (the hyperhomodesmotic level) for both these molecules shows that their reactions do not match the criteria set by them in their definition of the RC5 (hyperhomodesmotic) level. For instance at the RC5 level, in the case of cyclopentadiene, there are only two $H_3C−CH$ bonds in the reactants side, whereas there are four $H_3C−CH$ bonds in the products side. This example clearly illustrates how even for a simple hydrocarbon like cyclopentadiene, using predefined reactants and products in the construction of a thermochemical hierarchy, can lead to minor oversights. Consequently, the balance in the reaction energy is slightly affected. In fact, this may be responsible for the slight deterioration of the performance observed by Wheeler et al. at the RC5 level for cyclic molecules. A physical, connectivity-based approach, naturally following the chemical structure of an organic compound, precludes the occurrence of such minor issues.

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