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Accurate Thermochemistry for Organic Cations via Error Cancellation using Connectivity-Based Hierarchy

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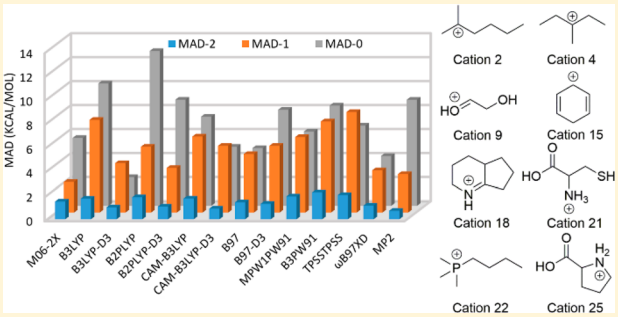
Supporting Information

ABSTRACT: Connectivity-Based Hierarchy (CBH) is an effective error-cancellation scheme for the determination of chemically accurate thermochemical properties of a variety of organic and biomolecules. Neutral molecules and open-shell radicals have already been treated successfully by this approach utilizing inexpensive computational methods such as density functional theory. Herein, we present an extension of the method to a new class of molecules, specifically, organic cations. Because of the presence of structural rearrangements involving hydrogen migrations as well as unusual structures such as bridged cations, the application of the standard CBH protocol to a test set of 25 cations leads to significant errors due to ineffective bond-type matching. We propose an adjusted protocol to overcome such limitations to achieve highly effective error cancellation. The modified CBH methods, in conjunction with a wide range of density functionals, reproduce G4 energies for the test set of organic cations accurately within 1−2 kcal/mol at a reduced computational cost.



1. INTRODUCTION

Organic cations are quintessential intermediates that play an important role in many diverse areas of chemical research such as catalytic reaction mechanisms, drug−receptor interactions, biosynthesis of natural products, and combustion chemistry. They have many unique bonding characteristics involving nonclassical structures, facile hydrogen migrations, unusual rearrangement pathways, and hypervalency. Because of their fleeting existence and high reactivity, theoretical investigations are pivotal to derive a clear understanding of the structure and function of organic cations. For example, a detailed knowledge of the thermochemical and kinetic parameters involving carbocations can improve our understanding of their role in complex multistep reactions in combustion chemistry. Similarly, pharmacological research could highly benefit from accurate enthalpies of cations to model drug reactivity in the human body. Currently, sophisticated ab initio calculations including high-order electron correlation effects are needed for the accurate determination of electronic structures and energies of these reactive species.

Modern quantum chemistry has developed a variety of advanced computational tools for the accurate computation of the bond energies of molecular systems such as carbocations. The most accurate methods, such as the gold-standard CCSD(T)[1] or composite models such as Gaussian-4 (G4),[2] predict energies very well but at a high computational cost and steep scaling. To avoid this scaling problem, faster methods, such as density functional theory (DFT), are often used. However, these results seldom achieve chemical accuracy (∼1 kcal/mol), and their inconsistency across different methods and systems makes them less reliable. Numerous new density functionals are being developed with the goal of achieving more universal applicability, but significant errors are still very prevalent.[3]

To overcome this performance deficiency, error-cancellation schemes, such as the isodesmic scheme initially introduced by Pople and co-workers in the 1970s,[4] have recently been revisited.[5] Particularly noteworthy in this context are the homodesmotic schemes, originally developed by George and co-workers,[6] and a range of related variants that have incorporated significant error cancellation by matching the bond types and hybridizations of the parent atoms. However, most such schemes proposed to achieve error cancellation are ambiguous or are only applicable to limited classes of systems such as hydrocarbons. To avoid such limitations, we introduced the connectivity-based hierarchy (CBH)[7] to calculate accurate thermodynamic properties of a broad range of organic molecules by providing a systematic hierarchy for error cancellation. CBH provides a well-defined universal scheme,

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is straightforward, easy to construct, and fundamental in its structure-based origin.

CBH has been used previously to determine highly accurate thermochemical properties of a range of medium-to-large closed-shell organic molecules, biomolecules such as amino acids and barbiturates,[8] as well as open-shell systems such as organic radicals.[9] More recently, it has been applied on a range of pericyclic and other organic reactions including rearrangement reactions.[10] A wide range of density functionals as well as wave function-based methods (e.g., MP2) have been utilized in these applications, showcasing the versatility of CBH.[11] The present paper extends the breadth of molecules applicable with CBH by evaluating its performance for a class of charged systems mentioned earlier, specifically, organic cations.

The success of CBH at producing thermochemical properties within 1−2 kcal/mol is due to its ability in the underlying schemes to maintain the bonding environment of the organic molecules. Cations possess many characteristics that make it challenging to achieve a high degree of error cancellation through the CBH schemes. This is partly due to efficient hydrogen migrations leading to structural rearrangements as well as unusual structures such as highly stable nonclassical (bridged) isomers. For example, the seemingly simple ethyl cation has a ground-state structure involving a bridged proton, and 1-propyl cation rearranges without a barrier to give 2-propyl cation. An additional potential drawback for organic cations is that reaction schemes in CBH are derived from an underlying valence-bond structure for the organic or biomolecular system. This can lead to ambiguity in systems with resonance structures or delocalized charges, as in some cations presented herein. A common practice in valence bond theory is to localize the charge onto an individual atom. In reality, the charge is delocalized across several surrounding atoms, and resonance forms can be drawn where the charge is shown localized on different atoms. In such cases involving multiple resonance structures, each structure will have its own set of CBH reaction schemes that depend on the location of the charge. This presents a challenging task to preserve the chemical nature on both sides of the CBH reaction schemes for some cationic systems (vide infra).

The construction of CBH schemes is performed in terms of well-defined rungs. A complete prescription for the construction of each CBH rung has been given previously.[9] CBH-0 corresponds to the isogyric scheme, where the molecule is separated into individual one heavy-atom (non-hydrogen) fragments. The current paper will focus on the performance of the next two rungs of CBH error-cancellation schemes: CBH-1 and CBH-2. The first rung (CBH-1) is identical to the isodesmic bond separation scheme[6,12] as it corrects for bond transformations, while CBH-2 is analogous to the hypo-homodesmotic bonding scheme,[13] correcting for medium-range effects such as hyperconjugation and protobranching. Previous publications on CBH have shown that the error can diminish further as a higher rung is included, due to increasingly better bond matching. Thus, CBH-3 (hyper-homodesmotic[14]) or CBH-4 can be used for more accurate energies, if needed.

2. COMPUTATIONAL DETAILS

A diverse group of density functional methods were chosen to assess the broad applicability of our methods. These functionals include: M06-2X hybrid functional,[15] the widely used hybrid functional B3LYP,[16,17] double-hybrid B2PLYP density functional,[18] long-range and dispersion-corrected ωB97XD functional,[19] long-range corrected CAM-B3LYP functional,[20] meta-hybrid TPSSh functional,[21] Perdew and Wang's nonlocal correlated hybrid functional B3PW91,[17] Becke's B97 hybrid functional,[22] and one-parameter hybrid functional mPW1PW91.[23] Grimme's dispersion corrections with Becke-Johnson damping (denoted as D3)[24] were applied to B3LYP, CAM-B3LYP, B97, and B2PLYP. In addition, a wave function-based level of theory (WFT) was also tested: second-order Møller−Plesset perturbation method, MP2.[25]

It is important to note that the scarcity of highly accurate experimental thermochemical properties for cations overburdens the careful assessment of the performance of theoretical methods. Instead, we elected to compare calculated enthalpies of different methods with their corresponding highly accurate enthalpies from composite G4 theory. Thus, reference G4 enthalpies were evaluated on all the systems and play the role of benchmark in our study. Optimizations of all molecules and fragments are performed with B3LYP/6-31G(2df,p) to match G4 composite method[2] with frequencies scaled by 0.9854, followed by single-point calculations with the larger 6-311++G(3df,2p) basis set. Unique reaction schemes for each CBH rung are generated based on the connectivity of the molecule, preserving a larger portion of the bonding environment at higher rungs. CBH reaction enthalpies at each rung are then evaluated with the selected method (e.g., DFT). The reaction enthalpy at a given rung is then combined with energies of corresponding daughter fragments (neutral molecules or cations) calculated at the higher level of theory, specifically, G4, to extrapolate to the enthalpy of the parent cation with much better accuracy. This is illustrated in eq 1, where reaction enthalpies (ΔCBH_n, n = 1,2) can be obtained from the energies of all the small CBH fragments at a given rung. The extrapolated G4 enthalpy found with CBH is denoted E(DFT:G4).

$$E(\text{DFT: G4}) = E(\text{DFT}) + [\Delta CBH_n(\text{G4}) - \Delta CBH_n(\text{DFT})] \quad (1)$$

Overall, G4 and DFT/WFT calculations on daughter fragments provide error corrections at each rung. An example of the CBH reaction schemes is given in the Supporting Information (Figure S1). All calculations were performed with the Gaussian-16 suite of computer programs.[26]

3. CBH-CAT25 TEST SET

A test set, referred to as **CBH-cat25**, of 25 organic cations ranging in size from five to nine heavy atoms is shown in Figure 1 (cations **C1−C25**). The test set includes carbocations containing various lengths of hydrocarbon chains (**C1−C8**), molecules featuring a positively charged oxygen (**C9−C10**), carbocations featuring ring structures (**C11−C15**), heterocycles including a positively charged nitrogen (**C16−C19**), a variety of amino acids bearing a charged nitrogen (**C20**, **C21**, **C23−C25**), and a phosphine cation bearing an alkyl chain (**C22**). The test set provides a wide range of functional groups and structural features to test the applicability of CBH on organic cations.

4. RESULTS AND DISCUSSION

a. Performance of CBH using the Standard Protocol for the Full Test Set. In previous applications of CBH for neutral organic molecules as well as organic radicals, a target accuracy of 2 kcal/mol was achieved at the CBH-2 rung for

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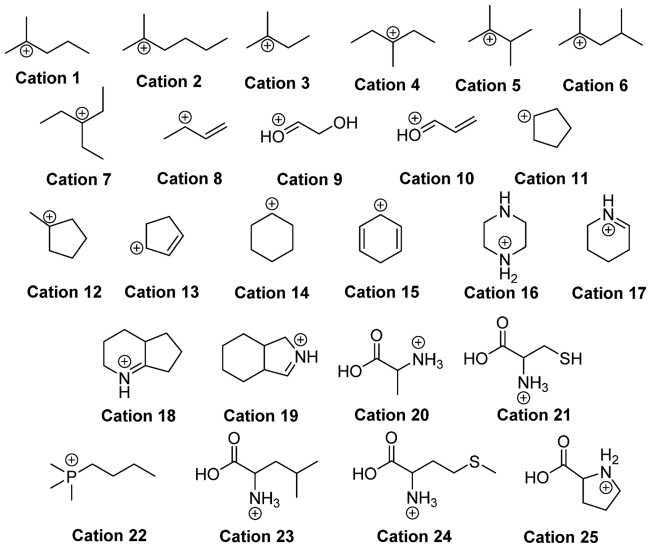

Figure 1. CBH-cat25 test set of organic cations (**C1−C25**) featuring a range of bonding environments.

almost all DFT functionals. The performance of MP2 was even better, less than 1 kcal/mol. The excellent performance for all DFT methods, independent of the nature of the functional, clearly demonstrates the outstanding error cancellation achieved at the CBH-2 rung. The performance of the DFT methods at the CBH-1 rung showed substantially larger deviations, suggesting that isodesmic schemes do not provide adequate error cancellation.

In contrast to the neutral molecules discussed above, the initial results using CBH schemes for the 25 cations in the test set via the standard protocol are substantially less accurate. Even at the CBH-2 rung, the mean absolute deviations (MAD), averaged over the 25 cations, range from 3 to 9 kcal/mol for different DFT functionals. Only the MP2 method achieves the target accuracy of less than 2 kcal/mol. The only functional that has a MAD of even 3 kcal/mol is M06-2X. All other functionals tested have MAD in the range of 5−9 kcal/mol. Some individual molecules have even larger deviations from G4, and the MAD with the CBH-1 rung is much worse. Clearly, using the standard protocol, error cancellation is not achieved, even at the CBH-2 rung.

A careful analysis of the different systems immediately reveals the reason for the deficiency of CBH for cations. All deviations stem from structural rearrangements of certain fragment cations that result in a mismatch between the structure and bonding in the rearranged cation from those in the parent cation. Clearly, the error cancellation due to the bond matching between the parent cation and the fragments is lost, resulting in poor performance. A well-defined strategy to maintain structural and bonding similarities between the parent cation and the fragment ions is addressed in the following section.

b. Treatment of Fragments that Rearrange. In the standard protocol for a given molecule, the CBH reaction schemes are first derived for the selected rungs, followed by an evaluation of the optimized geometries and energies of the daughter fragments. In studies involving related classes of molecules, the geometries and energies of the fragments that are already available can be obtained from a look-up table, avoiding many repetitive calculations on the same fragments derived from different parent systems. This protocol works well for neutral species and radicals, but some carbocations, particularly primary cationic species $CH_3CH_2^+$, $CH_3CH_2CH_2^+$, and $(CH_3)_2CCH_2^+$, are unstable as isolated fragments. Cation stability depends on the connectivity of the charged atom, and well-known effects, such as hyperconjugation, also play a key role. In particular, several primary carbocation fragments undergo hydrogen migration to lead to minima where the charged atom is in a secondary or tertiary environment. In our fragment primary cations, the ethyl cation rearranges to a bridged isomer, the 1-propyl cation rearranges to a secondary 2-propyl cation, and primary isobutyl cation $(CH_3)_2CHCH_2^+$ rearranges via hydrogen migration to the t-butyl cation $(CH_3)_3C^+$. Since the fundamental nature of CBH relies on matching bond types for the reaction schemes,[9] such rearrangements result in a poor balance in the chemical environment, yielding larger MADs.

Two potential strategies to preserve the bond types and connectivity are as follows: (a) symmetry-restricted optimizations and (b) extraction of the fragment ion from the optimized structure of the parent cation. The simplest strategy involves a symmetry-restricted optimization where the terminal $-CH_2$ group is rotated to a perpendicular plane effectively preventing hydrogen migration and suppressing the rearrangements. The resulting optimized structures (Figure S2) preserve the chemical environments of interest, maintaining the primary character of the cationic center, and are easily integrated into the CBH schemes. It is important, however, to note that symmetry-restricted optimization does not always lead to a minimum structure; that is, imaginary frequencies may be present. Since the thermal correction from the fragments are canceled between the lower level (B3LYP) and the high level (G4), imaginary frequencies, if present, do not play a role in the calculation of the parent molecular enthalpy.

Reaction schemes of 12 parent cations from **CBH-cat25** (**C1−C8** and **C11−C14**) involve the three rearranging daughter ions mentioned above. The MAD (averaged over all the methods) for CBH-2 using the standard protocol is compared to those with the symmetry-restricted protocol for these 12 cations in Table 1. There is a dramatic decrease in the deviations from G4 for most systems on going to the symmetry-restricted protocol. Overall, the MAD falls from over 6 to 1.65 kcal/mol. The effect of symmetry-restricted CBH for the different methods is shown in Figure 2.

Table 1. Mean Absolute Deviations[a] for CBH-2 Comparing Traditional CBH and Symmetry-Restricted CBH on Cations That Involve Rearranging Fragments

	traditional CBH	symmetry-restricted CBH
Cation 1	4.56	1.53
Cation 2	4.79	1.76
Cation 3	4.32	1.28
Cation 4	8.53	2.27
Cation 5	6.12	2.32
Cation 6	4.99	1.94
Cation 7	12.50	3.04
Cation 8	2.08	1.30
Cation 11	6.88	1.14
Cation 12	7.22	1.19
Cation 13	5.15	1.35
Cation 14	6.48	0.71
Total MAD	6.14	1.65

[a]In kcal/mol.

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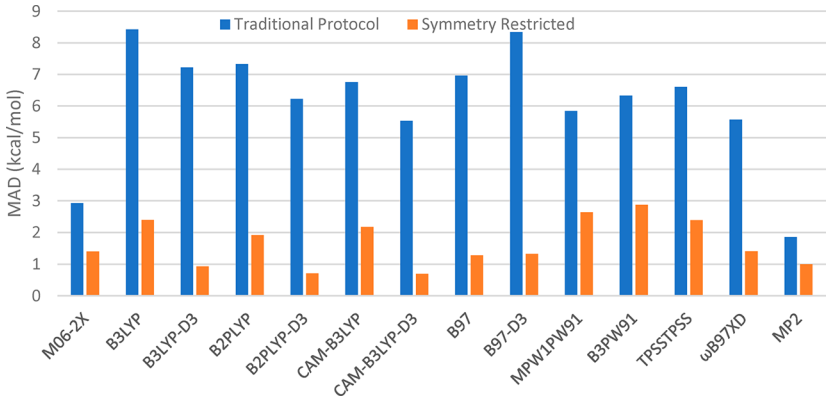

Figure 2. Comparison of MAD from CBH-2 reaction schemes for traditional (blue) and restricted-symmetry CBH (orange).

To check if there are performance imbalances related to the rearrangements of cationic fragments, the MAD is compared between cations containing rearranging fragments and the others that do not. As mentioned above, the MAD for the 12 cations was 1.65 kcal/mol with the symmetry-restriction protocol. The CBH-2 reaction schemes that do not involve the rearranging fragments has a MAD that is only slightly smaller, 1.29 kcal/mol. Both sets of MADs are under the target accuracy of 2 kcal/mol, clearly demonstrating the error-cancellation scheme is successful.

The cations included in the test set can be categorized into two distinct subclasses. On the one hand, cations **C1−C8** and **C11−C15** are all carbocations housing carbons with a positive formal charge and incomplete octet (three single bonds). On the other hand, when more electronegative atoms (nitrogen and oxygen) house the positive charge (**C9−C10** and **C16−C25**), there is a complete octet and the charge is more localized. The relative stability of cations with all complete octets is higher than carbocations in which the positively charged carbon does not have a full valence. Overall, the chemical environment is conserved more effectively in the fragments and reaction schemes where the charge is more localized, yielding smaller MAD from G4 composite method for the latter set.

c. Performance of All Methods for the Full Test Set. The first two rungs of CBH (CBH-1 and CBH-2) were applied to the whole test set, using symmetry-restricted optimizations when applicable, and benchmarked against CBH-0 calculated MADs. The MAD from G4 enthalpies for all methods are summarized in Table 2 and Figure 3.

All functionals performed within 2 to 9 kcal/mol compared to the enthalpies obtained with G4 theory at the CBH-1 rung. Many methods feature significant 2−7 kcal/mol improvements from the baseline of CBH-0, though some fare slightly worse. The smallest MAD with CBH-1 is obtained with M06-2X (2.54 kcal/mol) and the largest MAD with the TPSSTPSS functional (8.37 kcal/mol). The next rung up, CBH-2, improved the deviations dramatically, falling within 1−2 kcal/mol of G4 theory for all except B3PW91 and TPSSTPSS functionals. Accuracy trends for the methods are consistent between CBH-1 and CBH-2 schemes. In general, hybrid functionals tend to overestimate the enthalpies, while dispersion-corrected methods slightly underestimate the enthalpies. Dispersion-corrected methods are better than their nondispersion-corrected counterparts, suggesting larger molecules or molecules with long-range interactions could benefit from the use of CBH with dispersion-corrected functionals.

Table 2. Mean Absolute Deviations[a] for CBH-0, CBH-1, and CBH-2 Schemes

method	MAD-0	MAD-1	MAD-2
M06-2X	5.65	2.54	1.47
B3LYP	10.20	7.71	1.73
B3LYP D3	2.38	4.11	1.00
B2PLYP	12.90	5.47	1.84
B2PLYP-D3	8.84	3.70	1.07
CAM-B3LYP	7.42	6.32	1.74
CAM-B3LYP D3	4.91	5.55	0.89
B97	4.80	4.86	1.41
B97-D3	8.00	5.55	1.29
MPW1PW91	6.18	6.27	1.90
B3PW91	8.35	7.58	2.25
TPSSTPSS	6.67	8.37	2.02
ωB97XD	4.14	3.50	1.15
MP2	8.83	3.19	0.71
Total MAD	7.09	5.34	1.46

[a]In kcal/mol.

At the CBH-2 rung, the best-performing functionals are ωB97XD, CAM-B3LYP-D3, and B3LYP-D3, all giving a mean deviation of ∼1 kcal/mol relative to the G4 enthalpies over all the parent cations. The excellent performance of such dispersion-corrected functionals for the CBH-cat25 test set suggests that they may be versatile for the treatment of complex systems with CBH. Overall, MP2 performed best with a MAD of only 0.7 kcal/mol using the CBH-2 scheme.

These trends are consistent with previous results from other test sets. In previous work on neutral molecules and organic radicals, CBH-1 historically performed with MAD of 2−5 kcal/mol, while CBH-2 fell within 1−2 kcal/mol relative to G4. Similar results are reported here on a test set with more complex systems with newer bonding types.

d. Amines with Delocalized Charges. Another problem that can potentially cause an imbalance in the CBH error-cancellation scheme involves systems containing two or more distinct resonance structures and delocalized bonding (e.g., **C17−C19**). These molecules feature an imine functional group, shown with a resonance structure involving a positive charge localized on the nitrogen, as drawn in Figure 1 (represented in this section as **C17N$^+$−C19N$^+$**, corresponding to the valence-bond structure R−N$^+$H═CHR′). Alternatively, these molecules could be drawn as a resonance structure containing a single-bonded amine group with the positive charge shown localized on the connected carbon atom

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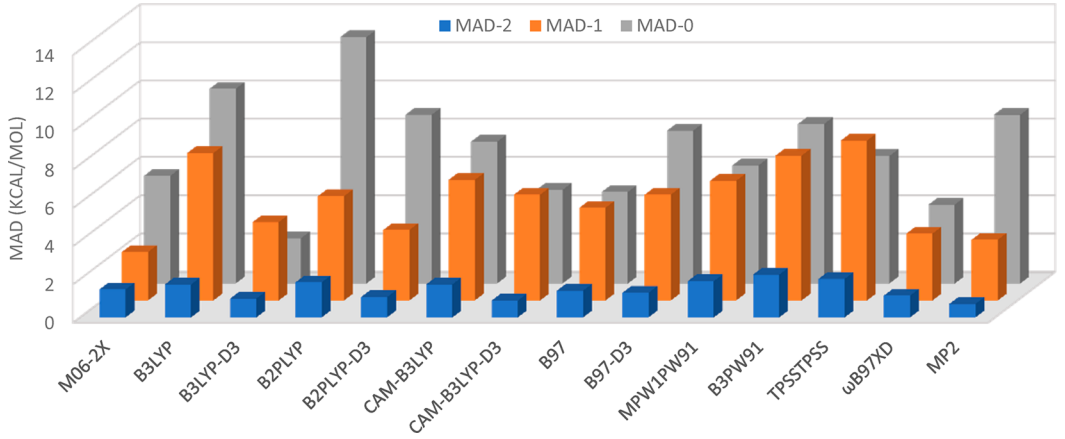

Figure 3. Mean absolute deviations from G4 (kcal/mol) for CBH-0 (gray), CBH-1 (orange), and CBH-2 (blue) reaction schemes for all methods.

(represented as **C17C$^+$−C19C$^+$**, corresponding to the valence-bond structure R−NH−C$^+$HR′). Each structure results in unique CBH reaction schemes and energies and may pose a problem because, in reality, the charge is shared by both carbon and nitrogen atoms.

We treated the three systems using both resonance structure-based reaction schemes and compared the results. The schemes based on the **N$^+$** resonance structure for **C17**, **C18**, and **C19** yielded MADs of 0.64, 1.79, and 1.72 kcal/mol, respectively, while the corresponding **C$^+$** structure-based schemes had MADs of 0.88, 3.03, and 1.47 kcal/mol, respectively. Overall, both schemes work reasonably well with the **N$^+$** schemes performing slightly better. Upon further inspection of the **C−N** bond lengths of the optimized structures, the difference in MAD between the two resonance structures is higher when the bond length is closer to either an optimized amine bond length (1.465 Å) or imine bond length (1.267 Å). In cations **C17** and **C19**, the **C−N** bond length is neither close to amine nor imine, so the MAD is less dependent on which resonance structure is chosen. Future strategies may include taking into consideration both resonance structures by paying closer attention to the optimized geometry of the parent molecule and the bond length in question. In addition, higher CBH rungs would capture the delocalized bonding more effectively by using larger fragments.

e. Comparison with Previous Results. The results shown in this paper for cations agree broadly with previous CBH data for closed-shell and open-shell complex organic molecules[9,14] and reaction enthalpies,[4] suggesting that there is no fundamental restriction for charged species. The trends in the performance of CBH for cations using different methods match previously observed trends for the neutral molecules, as compared in Table 3.

Overall, CBH-1 performed slightly worse than found in previous work.[9,14] This discrepancy is due to the inability of rung 1 fragments to accurately model the chemical environment of charged molecules. The maximum size of fragments in CBH-1 reaction schemes is two heavy atoms, while CBH-2 is normally three to four heavy atoms. Thus, CBH-2 can better model the charge delocalization across multiple atoms than CBH-1. CBH-2 for cations also performs slightly worse than for neutral molecules, though the MAD is within the target of 2 kcal/mol for most methods.

Table 3. Selected Mean Absolute Deviations (kcal/mol) for CBH-1 and CBH-2 Schemes Comparing Data Reported in This Study to Past Data

	previous work[9,14]		this work	
method	MAD-1	MAD-2	MAD-1	MAD-2
M06-2X[9]	2.73	1.73	2.54	1.47
B3LYP[14]	2.23	1.28	7.71	1.73
B2PLYP[9]	4.21	1.15	5.47	1.84
TPSSTPSS[9]	7.85	1.30	8.37	2.02
ωB97XD[14]	1.67	1.14	3.50	1.15

5. CONCLUSION AND SCOPE

The current study extends the CBH thermochemical hierarchy to a new family of systems, organic cations. Cations provide significant challenges to CBH methods due to rearrangements involving hydrogen migrations in some of the fragment ions. This imbalance in the bond-type matching of CBH leads to significant deviations using the standard protocol. Our strategy using symmetry-restricted geometries solves this problem, leading to MADs in the range of 1−2 kcal/mol for DFT methods and less than 1 kcal/mol for MP2. With our new findings, a more complete and robust toolbox for the CBH error-cancellation schemes is available. We recommend using CBH to perform accurate calculations of thermochemical properties involving any of the following species: closed-shell organic molecules, charged organic molecules, and open-shell organic radicals with low spin contamination. CBH-3 rungs and higher are expected to be more accurate and can be used as needed.

Finally, it is important to note that redundant calculations of the same fragments resulting from more than one parent molecule can be avoided using a look-up table of the fragment structures and energies. In particular, G4 fragment energies can be stored for commonly occurring fragments. Thus, the computational cost of finding the enthalpy of a new molecule is solely dependent on the calculation of the parent molecule with a given DFT method, enabling the calculation of accurate enthalpies of substantially larger molecules.

■ ASSOCIATED CONTENT

Supporting Information

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Sample CBH-0, CBH-1, and CBH-2 reaction schemes, optimized structures for rearranging fragments, reaction scheme deviations for the 25 cations in CBH-cat25 test set at various levels of theory, and the Cartesian coordinates of all the 25 cations (PDF)

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Notes

The authors declare no competing financial interest.

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