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Estimating Ring Strain Energies of Highly Substituted Cyclohexanes with the Semi-homodesmotic Approach: Why Substantial Ring Strain Exists for Nominally Tetrahedral Ring Carbon Atoms

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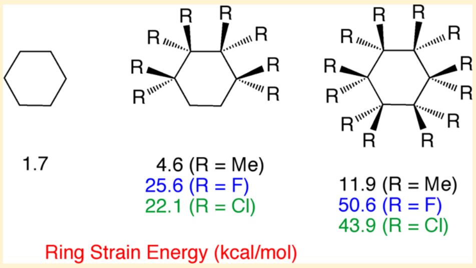
S Supporting Information



ABSTRACT: Estimation of ring strain energies (RSEs) of substituted cyclohexanes $c\text{-}C_6H_xR_{12-x}$ (R = F, Cl, Me; x = 0, 2, 4, 8, 10, 12) using homodesmotic reaction methods gives implausible results for highly substituted cases, particularly, $c\text{-}C_6R_{12}$. Prior work suggests that this stems from poorly canceled interactions between substituents on the acyclic reference molecules. We apply here our semi-homodesmotic approach that minimizes use of acyclic references and ensures cancellation of intramolecular substituent interactions. The approach provides RSEs that are more consistent with chemical intuition, although they are higher than expected for "strain-free" cyclohexanes. The RSE for $c\text{-}C_6Me_{12}$ is predicted to be 11.9 kcal mol^{-1}. RSEs for halogenated rings rise significantly from 8−9 kcal mol^{-1} for $c\text{-}1,1,2,2\text{-}C_6H_8R_4$ to 44−50 kcal mol^{-1} for $c\text{-}C_6R_{12}$ (R = F, Cl). The increase, and accompanying observation of larger RSEs for "adjacent CR_2" systems, can be tied to increased bond distances in the rings upon progressive substitution. The sizable RSE for perchlorocyclohexane suggests that it may be susceptible to ring-opening reactions, a facet of its chemistry that is currently unexplored.

INTRODUCTION

Cyclohexanes are viewed as archetypal "strain-free" rings,[1] owing to the near-tetrahedral environments around ring carbon atoms. That cyclohexane has no ring strain is a key concept found in beginning organic chemistry textbooks, and thermodynamic databases such as that of Benson's rules give the ring strain energy (RSE) of cyclohexane as essentially zero.[2] This arises conceptually because RSE, while not a direct physical measurable, is seen as a combination of (plausibly) measurable strain energies such as angle (Baeyer) strain, torsional (Pitzer) interaction strain, and transannular interaction strain.[3,4] For cyclohexanes, all three are thought to be negligible: the first because of the near-tetrahedral ring carbon geometries, the second because of the staggered orientations of axial/equatorial substituents on adjacent ring carbons, and the third because the rings span sufficiently large surface areas that substituents in transannular positions do not interact. While experimental additivity schemes[5] and computational studies have suggested for decades that RSE ($c\text{-}C_6H_{12}$) = 1.4−2.2 kcal mol^{-1} rather than zero,[6−11] that cyclohexanes might have RSEs *significantly* larger than zero lies outside of mainstream thought.

That said, some problematic predictions of RSEs of perhalocyclohexanes have appeared in the literature. Using various homodesmotic reaction calculations[12] comparing the energies of such rings with those of acyclic reference molecules, Liebman et al.[13] and Mosquera et al.[14] predicted RSE ($c\text{-}C_6F_{12}$) ranging from 78 to 0 kcal mol^{-1} and RSE ($c\text{-}C_6Cl_{12}$) ranging from 103 to −39 kcal mol^{-1}. Insofar as RSEs are meant to describe the energetic effect of distorting the environment of carbonic moieties when they are forced into a ring, these ranges are obviously far too broad to be physicochemically useful. They do not point to credible, molecularly unique RSE values that could be supported by thermochemical experiments. Moreover, they include the worrisome prediction of negative RSEs. While a negative RSE implies simply that the cycle of interest is more stable than the acyclic reference molecules,[15] it is difficult to see why, for example, $c\text{-}C_6Cl_{12}$ would be 39 kcal mol^{-1} more stable than six molecules of $n\text{-}C_3Cl_8$, as suggested.[13] Protobranching[16] is not an issue here, as both reactant and products incorporate six protobranches. Furthermore, as we show below, a negative RSE for $c\text{-}C_6Cl_{12}$ is inconsistent with the structural changes (and with QTAIM data) predicted as one progressively substitutes hydrogen on cyclohexanes with chlorine.

We previously criticized reports of implausible RSEs for cyclopropanes and cyclobutanes determined using homodesmotic reaction approaches because use of acyclic (or sometimes cyclic) reference molecules did not properly cancel intramolecular interactions and because this problem increased with the number of substituents (and in turn the number of interactions).[17,18] We provided an alternative semi-homodesmotic approach that properly canceled intramolecular interactions by using un-, mono-, and disubstituted cycloalkanes as reference molecules. The approach is semi-homodesmotic because a sum of uncanceled bond energies is treated as a parameter that can be estimated from comparison of absolute ring energies and because RSEs of reference cycloalkanes are

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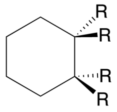
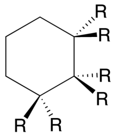
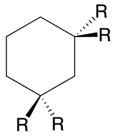
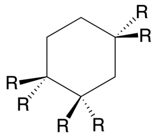
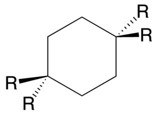
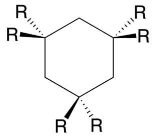
Table 1. RSEs for Tetra- and Hexasubstituted Cyclohexanes (kcal mol^{-1}) from Homodesmotic Reactions in Figure 1 with 6-311+G(d,p) Basis Set

	R	Reaction	Model Chemistry			R	Reaction	Model Chemistry	
			M06-2x	MP2				M06-2x	MP2
	Me	1	6.7	4.6		Me	1	17.8	14.8
		2	1.1	–0.8			2	11.3	8.3
		3	4.8	3.2			3	–2.5	–4.8
		4	–2.8	–3.7			4	–8.2	–9.6
	F	1	9.7	9.4		F	1	22.9	22.4
		2	3.3	2.5			2	16.7	15.2
		3	10.1	9.2			3	2.4	1.4
		4	3.3	2.3			4	2.7	1.4
	Cl	1	7.7	1.2		Cl	1	23.4	12.2
		2	0.2	–3.5			2	16.6	8.4
		3	9.2	4.3			3	–6.1	–9.7
		4	0.4	0.4			4	–6.5	–7.0
	Me	1	5.3	3.0		Me	1	9.6	6.5
		2	3.7	1.3			2	3.0	0.1
		3	–1.6	–3.4			3	–0.3	–3.1
		4	–4.8	–6.1			4	–6.8	–8.2
	F	1	4.8	4.4		F	1	15.5	15.1
		2	5.3	4.2			2	9.3	7.9
		3	–1.9	–2.5			3	9.5	7.5
		4	–1.4	–2.5			4	2.6	1.5
	Cl	1	4.5	–1.0		Cl	1	14.6	5.5
		2	6.1	1.1			2	7.8	1.8
		3	–4.4	–7.3			3	8.5	3.7
		4	–3.4	–4.3			4	–1.9	–1.4
	Me	1	2.8	0.6		Me	1	11.5	7.8
		2	1.1	–1.1			2	8.8	5.1
		3	–1.7	–3.9			3	2.2	–1.1
		4	–1.8	–2.9			4	–5.3	–7.6
	F	1	2.3	2.1		F	1	13.5	12.6
		2	2.9	2.0			2	14.2	12.2
		3	3.2	1.6			3	7.0	5.3
		4	3.4	2.1			4	0.0	–1.4
	Cl	1	–0.4	–5.8		Cl	1	15.2	5.6
		2	1.3	–3.7			2	17.6	8.7
		3	2.3	–2.1			3	7.5	1.0
		4	2.0	0.5			4	–3.0	–5.6

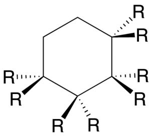
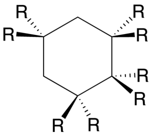
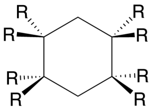
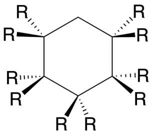
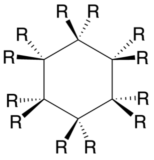
determined from homodesmotic reactions that use acyclic reference molecules. Nonetheless, the semi-homodesmotic approach gave RSE predictions for highly substituted cyclopropanes and cyclobutanes that made physical sense and were consistent with limited experimental data and with QTAIM data.

We report here application of the semi-homodesmotic approach to RSE predictions for polysubstituted cyclohexanes containing methyl, fluoro, and chloro substituents. We find, as before for smaller rings, that homodesmotic methods that use acyclic reference molecules fail for highly substituted cyclohexanes, giving RSE predictions that span a sizable (and so useless) range and that in some cases are nonphysical. In contrast, the semi-homodesmotic approach gives RSE predictions that make physical sense. We find that highly substituted cyclohexanes exhibit RSEs sizably larger than zero, particularly when halide-substituted, and provide a rationale for the phenomenon stemming from the effect of vicinal substituent proximity on ring bond distances.

■ COMPUTATIONAL METHODS

Optimizations and frequency analyses were performed using the Gaussian (G09)[19] suite. All molecules examined were fully optimized without constraints (save that cyclohexanes were restricted to chair conformers) at either the HF/6-31+G(d,p) or the M06-2X[20]/6-31+G(d) level. A sizable integration grid (Gaussian keyword INT(UltraFineGrid)) was used in all cases. Analytical frequency analyses at these levels demonstrated that the structures were minima (no imaginary frequencies) and provided zero point energies (ZPEs), which were appropriately scaled[21,22] when used to calculate RSEs listed in Tables 1 and 2. Starting structures for some acyclic reference

Table 2. RSEs for Octa-, Deca-, and Dodecasubstituted Cyclohexanes (kcal mol^{-1}) from Homodesmotic Reactions in Figure 1

	R	Reaction	Model Chemistry	
			M06-2x	MP2
	Me	1	28.0	23.9
		2	16.5	12.6
		3	12.7	9.1
		4	−18.7	−20.6
	F	1	37.6	36.7
		2	24.6	22.5
		3	24.7	22.1
		4	4.3	2.4
	Cl	1	40.4	23.6
		2	25.1	13.8
		3	25.5	16.0
		4	−11.0	−12.6
	Me	1	23.3	18.9
		2	15.7	11.5
		3	0.6	−3.0
		4	−12.2	−14.5
	F	1	33.1	31.9
		2	27.0	24.4
		3	12.8	10.4
		4	5.7	3.9
	Cl	1	35.0	18.4
		2	28.9	15.5
		3	6.7	−1.9
		4	−4.8	−7.6
	Me	1	16.7	12.8
		2	9.2	5.3
		3	2.7	−0.4
		4	−17.1	−18.9
	F	1	30.7	29.8
		2	24.6	22.3
		3	16.9	15.5
		4	11.0	9.8
	Cl	1	34.0	18.3
		2	27.8	15.4
		3	15.8	5.4
		4	8.1	4.8
	Me	1	41.3	35.9
		2	28.8	23.7
		3	13.7	9.5
		4	−26.9	−29.2
	F	1	56.6	54.7
		2	43.7	40.3
		3	29.0	26.4
		4	9.4	6.9
	Cl	1	63.5	40.2
		2	48.9	31.3
		3	24.7	11.5
		4	−10.7	−15.6
	Me	1	67.2	60.2
		2	49.8	43.2
		3	26.2	20.7
		4	−19.2	−22.8
	F	1	83.7	80.7
		2	64.0	59.3
		3	42.3	38.3
		4	22.7	19.5
	Cl	1	96.2	65.2
		2	73.1	50.4
		3	36.8	20.9
		4	−1.0	−9.0

molecules were taken from the literature.[23−25] Where literature data were not available, either multiple conformers spanning conformational space were optimized to determine that of lowest energy or a pseudohelical structure based on that of the analogous polyfluoroalkane was used. All structures were then reoptimized at the model/6-311+G(d,p) level (model = M06-2X, MP2[26]); frequency analyses were rerun for the density functional theory cases to ensure that the stationary point structures were still minima. CBS-QB3[27,28] composite energy calculations used the M06-2X/6-311+G(d,p)-optimized structures as starting points.

Critical point, bond path, and bond path angle calculations were performed using M06-2X/6-311+G(d,p) (6d,10f) wave functions and the AIMAll program,[29] which implements the quantum theory of atoms in molecules (QTAIM) theory developed by Bader and coworkers.[30−32] Structures optimized using the M06-2X/6-311+G(d,p) (5d,7f) spherical basis set approach above were reoptimized using the Cartesian basis set functions[33] before running the QTAIM jobs; this had no impact on structural parameters. Below, we distinguish geometric bond distances—the conventional ones used to define molecular geometries—from bond path distances. Bond path distances correspond to the distance along the path of maximum electron density between atomic nuclei that contain a QTAIM bond critical point; bond critical points correspond to positions between atomic nuclei where an entity traveling the path away from one nucleus finds electronic density equilibrium between that nucleus and another. QTAIM data have been shown to correlate with RSEs, often better than geometric data do.[14,34,35]

■ RESULTS AND DISCUSSION

Homodesmotic RSE Predictions. As before,[17,18] we first show that homodesmotic approaches provide implausible RSEs. RSEs determined for tetra-, hexa-, octa-, deca-, and dodecasubstituted cyclohexanes using the homodesmotic reactions in Figure 1 appear in Tables 1 and 2. Reaction 1 is a Bachrach-style group equivalent reaction[36] that minimizes nearest

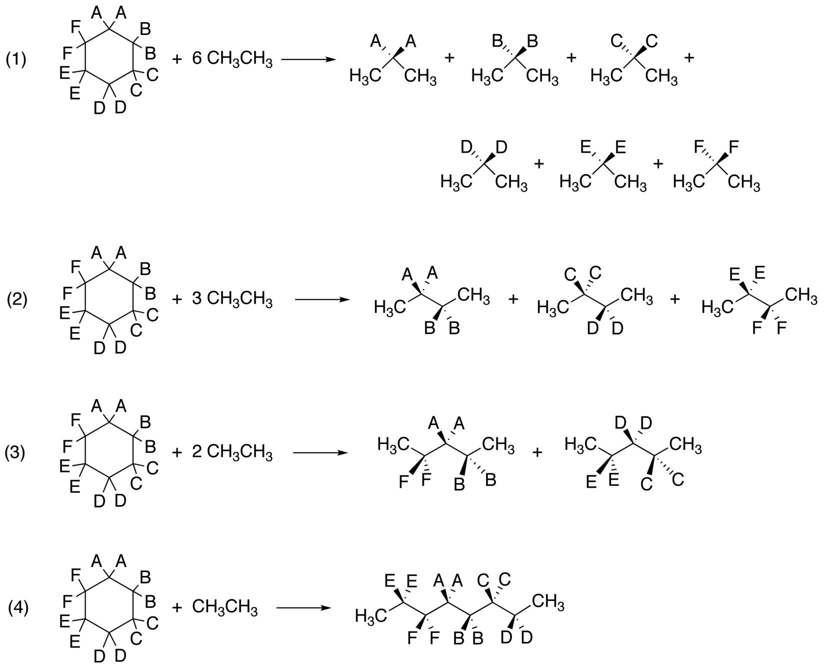


Figure 1. Skeleton homodesmotic reactions for estimating RSEs of cyclohexane and substituted cyclohexanes.

neighbor interactions in the acyclic reference molecules; reactions 2−4 preserve various degrees of ring nearest neighbor interactions using progressively longer chain reference molecules. If incomplete cancellation of nearest neighbor interactions dominates errors in RSE determinations, one expects that, in general, RSEs will become progressively more negative across reactions 1 to 4. In the discussion to follow, we will focus on MP2-determined RSEs, as these are typically closer to zero (and so more in keeping with lore as to what RSEs for cyclohexanes should be) than are M06-2X-determined RSEs.

The RSE values in the tables indeed decrease nonuniformly between reactions 1−4, particularly for the more highly substituted cases. One sees that predicted RSEs span a sizable range even for the modestly substituted *c*-1,1,2,2-$C_6H_8R_4$ rings (R = Me, 8.3 kcal mol^{-1}, R = F, 7.1 kcal mol^{-1}),[37] and that this range increases with substitution, reaching values of 81.0 kcal mol^{-1} (R = Me), 61.2 kcal mol^{-1} (R = F), and 74.2 kcal mol^{-1} (R = Cl) for *c*-C_6R_{12}. These ranges are obviously too large to allow determination of "correct" RSEs or to allow use of RSE as a chemically significant concept. Moreover, it is apparent that several homodesmotic calculations, particularly those for reaction 4 and when R = Me or Cl, give RSEs that are too negative to be characterized as "zero with some numerical error". We contend, as before,[17,18] that this arises from multiple instances of inadequate cancellation of intramolecular substituent−substituent interactions. Even apparently trivial interactions can exhibit significant repulsion energies that can bias a homodesmotic calculation.[16,23,38,39]

Ironically, given the last point, another criticism of the homodesmotic RSE data is that predictions for highly substituted cyclohexanes from group equivalent reaction 1 seem implausibly large. As a crude example, consider the reaction 1 RSEs for *c*-1,1,2,2-$C_6H_8R_4$ versus those for *c*-1,1,2,2,4,4,5,5-$C_6H_4R_8$. The latter resembles the former in that it has isolated sets of vicinally disubstituted ring carbons, the difference being that it has two sets of these rather than one. One might expect therefore RSE (*c*-1,1,2,2,4,4,5,5-$C_6H_4R_8$) ≈ 2 RSE (*c*-1,1,2,2-$C_6H_8R_4$). In fact, for R = Me and F, the ratio is closer to 3, and for R = Cl it is ca. 16. Examples relying more on chemical intuition arise from the RSEs predicted by reaction 1 for the R = Me deca- and dodecasubstituted cyclohexanes (35.9 and 60.2 kcal mol^{-1}, respectively). Both values exceed those for cyclopropane and cyclobutane,[2] even though the latter contain far more highly distorted ring carbon geometries. The RSE predicted for *c*-C_6Me_{12} exceeds that for cyclopropene, as well,[2] even though the latter contains highly distorted sp^2 ring carbons. Assuming that distorted ring carbon geometries are the largest contributor to RSE, it seems unlikely that the large values predicted by reaction 1 can be correct. Similar arguments can be made for the fluoro- and chlorosubstituted cyclohexanes. In particular, we note that a calculation based on experimental thermochemical data suggested RSE (*c*-C_3F_6) = 83 ± 6 kcal mol^{-1},[40] a value the semi-homodesmotic approach supported. Table 2 shows that reaction 1 predicts RSE (*c*-C_6F_{12}) = 80.7 kcal mol^{-1}, that is, equivalent to that of perfluorocyclopropane. Again, presuming that one can draw conclusions from ring carbon geometries, it is chemically counterintuitive that the RSE for a persubstituted cyclohexane should be identical to that for a persubstituted cyclopropane.

The data in Tables 1 and 2 show other noteworthy trends. Foremost is the relationship between substitution pattern and RSE. Comparing, for example, reaction 1 RSEs for the three octasubstituted cyclohexanes, one sees that as the number of adjacent disubstituted ring carbons decreases (i.e., from 4 in *c*-1,1,2,2,3,3,4,4-$C_6H_4R_8$ to 3 in *c*-1,1,2,2,3,3,5,5-$C_6H_4R_8$ to 2 in *c*-1,1,2,2,4,4,5,5-$C_6H_4R_8$), the predicted RSE decreases. The comparison is broadly consistent across reactions 1−4 and for all three substituent types, although exceptions exist. The implication, at least in part, is that adjacent substituted ring carbons deform the ring and increase RSE. We will explore this hypothesis further below in the context of semi-homodesmotic RSEs.

Second, as seen previously for cyclopropanes and cyclobutanes, RSE values increase with electronegativity of the substituents, Me < Cl < F, although this holds well only for

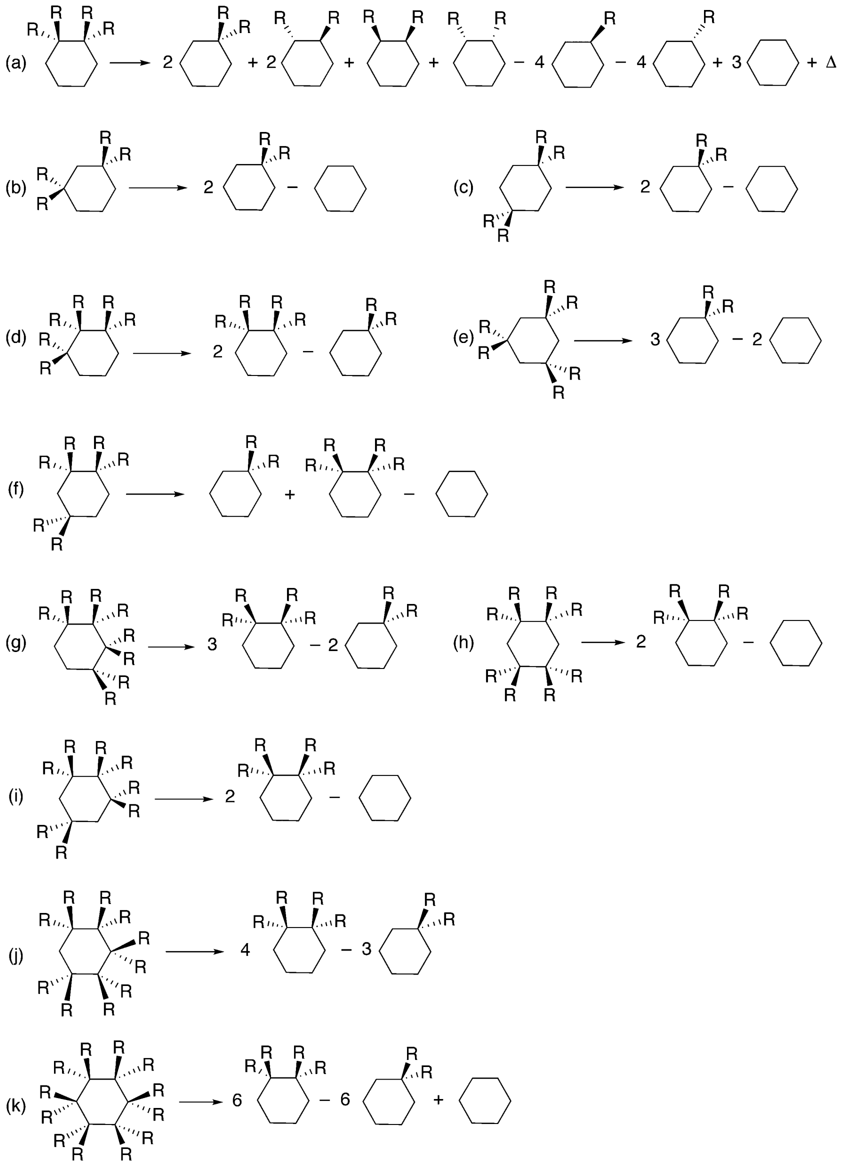


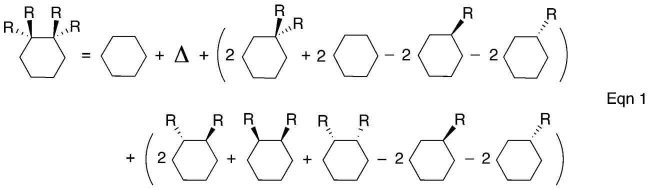
Figure 2. Skeleton reactions for estimating RSEs of substituted cyclohexanes using the semi-homodesmotic approach.

highly substituted cyclohexanes. For less substituted ones, fluorinated cyclohexanes still exhibit the largest RSEs, but distinctions between methyl- and chlorocyclohexanes are less clear. This probably reflects competition between the effects of electronegativity (increased RSEs) and substituent steric size (decreased RSEs when computed homodesmotically). Again, this will be addressed below in discussing semi-homodesmotic RSEs.

Semi-homodesmotic Predictions. We described the semi-homodesmotic approach to estimating RSEs in previous work.[17,18] Briefly, the approach employs un-, mono-, and disubstituted cyclic reference molecules, with reactions designed to cancel intramolecular interactions rather than bond types. Required RSEs of the cyclic reference molecules are determined from group equivalent reactions. Using lightly substituted reference molecules and group equivalent reactions provides RSEs that suffer least from errors due to uncanceled intramolecular interactions between substituents. The improperly canceled bond energies inherent in the semi-homodesmotic approach are incorporated into a parameter Δ, which is estimated as the difference in absolute energies of the rings in reaction (a), Figure 2. The advantage of the approach lies in its removal of errors owing to intramolecular interactions between substituents in reference molecules and in modeling the local carbon ring geometries closely by using identically sized rings as reference molecules. The disadvantage lies in the necessity for the Δ parameter and our inability to be certain that we have estimated it correctly. Experience has suggested that $\Delta \approx 0$ kcal mol^{-1}, but we have seen it as large as 6 kcal mol^{-1} for chlorosubstituted rings.[18] Therefore, we tend to view it as an error bar for each type of substituent and assume that differences in RSEs smaller than Δ cannot be proven different.

Semi-homodesmotic reactions for estimating RSEs of geminally disubstituted tetra- and more highly substituted cyclohexanes appear in Figure 2.[41] Since the 1,1,2,2-tetrasubstituted cyclohexanes are used often in calculations for more highly substituted rings, it is worth rearranging reaction (a) to give eq 1 to illustrate a conceptual decomposition of the RSEs.

Equation 1 indicates that the RSE of the tetrasubstituted cyclohexane can be viewed as the RSE of cyclohexane corrected by addition of the Δ value (both of which should be near zero)



Eqn 1

and two RSE-based terms. The first term involves RSEs affected by RCR angular interactions, while the second involves RSEs affected by RCCR torsional interactions. We clarify here that these terms do not represent uncanceled intramolecular interactions in the equation (the semi-homodesmotic approach is specifically designed to ensure overall cancellation of such interactions) but instead describe one non-unique way of grouping rings where the interactions of each type are most pronounced. The first term is likely to be close to zero, while the second is likely to be positive. Thus, one expects RSE (c-1,1,2,2-$C_6H_8R_4$) > RSE (c-C_6H_{12}), with the degree of increase dependent on the degree to which torsional and angular interactions increase the RSEs of the disubstituted cyclohexanes. Equation 1 also points out that an error in estimating RSE of any particular mono- or disubstituted ring is likely to be damped by the multiple RSEs present in each term. Nonetheless, since RSEs for modestly substituted cyclohexanes are likely to be near zero, yet their differences from zero will largely determine the RSEs of highly substituted rings, it is crucial to employ as trustworthy and functional a set of calculations as resources allow. We therefore modified our usual semi-homodesmotic practice in two ways. We chose to use a modified version of the group equivalent reactions 1, incorporating extra methylene groups into the calculation and using eclipsed "W" structures for pentane and substituted pentanes (Scheme 1). This better accounted for 1,3-interactions between substituents. We also employed the CBS−QB3 composite model in order to minimize errors in the absolute energies; the model approximates a CCSD(T)/large basis set calculation and so is likely to be more accurate than the M06-2X or MP2 calculations. The resulting data appear in Table 3. These were used to calculate RSEs using the semi-homodesmotic approach (Table 4).

One sees in Table 3 that RSEs for the modestly substituted cyclohexanes indeed differ only slightly from that of cyclohexane, which the CBS−QB3 model chemistry and homodesmotic reaction suggest is 1.7 kcal mol^{-1}, in line with the 1.4−2.3 kcal mol^{-1} range mentioned above.[6−11] For any type of substituted cyclohexane, the values trend as R = F > R = Cl > R = Me, implying that electronegativity differences dominate steric issues for these. The Δ values suggest an overall error bar of ca. 2 kcal mol^{-1}, so we start with the assumption that RSEs that differ by less than this are equal. Thus, the range for "strain-free" rings is the RSE for cyclohexane plus/minus 2 kcal mol^{-1}, or 0−4 kcal mol^{-1}.

Table 3. Group Equivalent RSE Data (CBS−QB3 Composite Model, kcal mol^{-1}) for Un-, Mono-, and Disubstituted Cyclohexanes Used To Calculate RSEs Using the Semi-homodesmotic Approach

	RSE		
c-C_6H_{12}	1.7		
	R		
	Me	F	Cl
c-ax-1-$C_6H_{11}R$	1.7	1.7	1.7
c-eq-1-$C_6H_{11}R$	−0.2	1.6	1.4
c-ax,ax-1,2-$C_6H_{10}R_2$	1.6	3.8	2.6
c-ax,eq-1,2-$C_6H_{10}R_2$	0.6	4.3	3.9
c-eq,eq-1,2-$C_6H_{10}R_2$	−1.1	4.2	3.7
c-1,1-$C_6H_{10}R_2$	−0.5	1.0	0.9
Δ	1.5	−1.3	−0.8

Table 4. RSEs (kcal mol^{-1}) Calculated Using the Semi-homodesmotic Approach

	R		
	Me	F	Cl
c-1,1,2,2-$C_6H_8R_4$	1.2	9.2	8.0
c-1,1,3,3-$C_6H_8R_4$	−2.7	0.3	0.2
c-1,1,4,4-$C_6H_8R_4$	−2.7	0.3	0.2
c-1,1,2,2,3,3-$C_6H_6R_6$	2.9	17.4	15.0
c-1,1,2,2,4,4-$C_6H_6R_6$	−1.0	8.5	7.2
c-1,1,3,3,5,5-$C_6H_6R_6$	−4.9	−0.3	−0.5
c-1,1,2,2,3,3,4,4-$C_6H_4R_8$	4.6	25.6	22.1
c-1,1,2,2,3,3,5,5-$C_6H_4R_8$	0.7	16.7	14.3
c-1,1,2,2,4,4,5,5-$C_6H_4R_8$	0.7	16.7	14.3
c-1,1,2,2,3,3,4,4,5,5-$C_6H_2R_{10}$	6.3	33.8	29.1
c-C_6R_{12}	11.9	50.6	43.9

Before examining the RSEs in Table 4 by substituent type, we note some general points. RSE (c-1,1,3,3,5,5-$C_6H_6R_6$) ≈ 0 kcal mol^{-1} regardless of the nature of R. It can be inferred from this that isolated CR_2 fragments (that is, fragments adjacent only to CH_2 fragments) do not contribute to increased ring strain. This is supported by several observations. First, RSE (c-1,1-$C_6H_{10}R_2$) ≈ 0 kcal mol^{-1} for all substituent types. Second, RSE (c-1,1,3,3-$C_6H_8R_4$) = RSE (c-1,1,4,4-$C_6H_8R_4$) ≈ 0 kcal mol^{-1} for all substituent types.[42] Third, RSE (c-1,1,2,2,4,4-$C_6H_6R_6$) ≈ RSE (c-1,1,2,2-$C_6H_8R_4$) and RSE (c-1,1,2,2,3,3,5,5-$C_6H_4R_8$) ≈ RSE (c-1,1,2,2,3,3-$C_6H_6R_6$). Likely related is that the more separated CR_2 fragments are, the smaller the RSE. This is most clearly seen across the (c-1,1,2,2-$C_6H_8R_4$), (c-1,1,3,3-$C_6H_8R_4$)/(c-1,1,4,4-$C_6H_8R_4$) series,[42] where the RSEs drop detectably, and also holds for the hexa- and octasubstituted cyclohexanes. We explore the underpinnings for these observations below.

RSEs of Methylcyclohexanes c-$C_6H_xMe_{12-x}$. As mentioned above, it is worth decomposing RSE (c-1,1,2,2-$C_6H_8R_4$)

Scheme 1

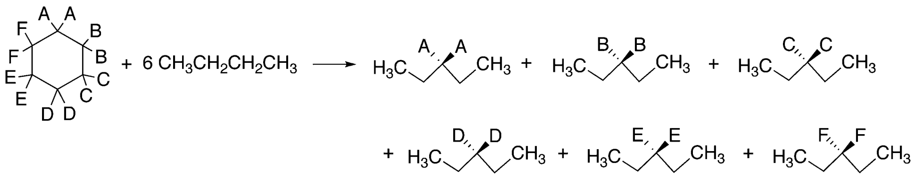


Table 5. Ring $R_2C{-}CR_2$, $R_2C{-}CH_2$, and $H_2C{-}CH_2$ Geometric Bond Distances and Bond Path Distances (Å) for Some Highly Symmetric Substituted Cyclohexanes

	MP2/6-311+G(d,p) geometric bond distance			M06-2X/6-311+G(d,p) bond path distance		
	$R_2C{-}CR_2$	$R_2C{-}CH_2$	$H_2C{-}CH_2$	$R_2C{-}CR_2$	$R_2C{-}CH_2$	$H_2C{-}CH_2$
c-C_6H_{12}			1.532			1.531
c-C_6F_{12}	1.546			1.546		
c-C_6Cl_{12}	1.590			1.597		
c-C_6Me_{12}	1.593			1.598		
c-1,1,3,3,5,5-$C_6H_6F_6$		1.517			1.518	
c-1,1,3,3,5,5-$C_6H_6Cl_6$		1.529			1.531	
c-1,1,3,3,5,5-$C_6H_6Me_6$		1.541			1.542	
c-1,1,4,4-$C_6H_8F_4$		1.513	1.532		1.514	1.530
c-1,1,4,4-$C_6H_8Cl_4$		1.523	1.530		1.525	1.531
c-1,1,4,4-$C_6H_8Me_4$		1.539	1.532		1.540	1.531

into components to determine which interactions exhibit the largest effect. The data (Supporting Information) give [RSE (*c*-C_6H_{12}) + Δ] = 3.1 kcal mol^{-1}, *E*(angular term) = −0.7 kcal mol^{-1}, and *E*(torsional term) = −1.3 kcal mol^{-1}. The intramolecular interaction terms are nearly negligible; the largest contributor to RSE (*c*-1,1,2,2-$C_6H_8R_4$) is [RSE (*c*-C_6H_{12}) + Δ], to which each component contributes approximately equally. Consequently, RSE (*c*-1,1,2,2-$C_6H_8R_4$) is small, so only when this value is multiplied by a sizable coefficient will RSEs of more highly substituted methylcyclohexanes become significant.

Confirming this, it is clear from the data in Table 4 that methyl substitution has relatively little impact on RSE. Assuming that the range mentioned above holds, and that small negative RSEs are functionally identical to RSE = 0 kcal mol^{-1}, only *c*-1,1,2,2,3,3,4,4-$C_6H_4Me_8$, *c*-1,1,2,2,3,3,4,4,5,5-$C_6H_2Me_{10}$, and *c*-C_6Me_{12} exhibit RSEs distinctly different from that of cyclohexane. These combine significant substitution with the pattern that all CMe_2 fragments are adjacent (giving contiguous $Me_2C{-}CMe_2$ ring bonds). Given our comments above, it is worth noting that RSE (*c*-C_6Me_{12}) = 11.9 kcal mol^{-1} is far smaller than that predicted by homodesmotic reaction 1 (>60 kcal mol^{-1}), and so it seems to be more reasonable.

One sees, comparing RSEs for the five "adjacent CMe_2" polymethylcyclohexanes, that they increase regularly by 1.7 kcal mol^{-1} until reaching *c*-C_6Me_{12}, whereupon RSE (*c*-C_6Me_{12}) ≈ 2 RSE (*c*-1,1,2,2,3,3,4,4,5,5-$C_6H_2Me_{10}$). Inspection of the relevant reactions (d), (g), (j), and (k) explains this. For the first three, RSE increases linearly each step by [RSE (*c*-1,1,2,2-$C_6H_8Me_4$) − RSE (*c*-1,1-$C_6H_{10}Me_2$)] = 1.2 − (−0.5) = 1.7 kcal mol^{-1}. However, between the decamethyl- and dodecamethylcyclohexanes, the increase is [2RSE (*c*-1,1,2,2-$C_6H_8Me_4$) + RSE (*c*-C_6H_{12}) − 3RSE (*c*-1,1-$C_6H_{10}Me_2$)] = 2(1.2) + 1.7 − 3(−0.5) = 5.6 kcal mol^{-1}. This could be overestimated; if one assumes RSE (*c*-1,1-$C_6H_{10}Me_2$) = 0 kcal mol^{-1}, in keeping with comments above, the RSEs for the series are RSE (*c*-1,1,2,2,3,3-$C_6H_6Me_6$) = 2.4 kcal mol^{-1}, RSE (*c*-1,1,2,2,3,3,4,4-$C_6H_4Me_8$) = 3.6 kcal mol^{-1}, RSE (*c*-1,1,2,2,3,3,4,4,5,5-$C_6H_2Me_{10}$) = 4.8 kcal mol^{-1}, and RSE (*c*-C_6Me_{12}) = 8.7 kcal mol^{-1}. These are not drastically different from the RSEs in Table 4.

RSEs of Fluorocyclohexanes *c*-$C_6H_xF_{12-x}$. In contrast to the methylcyclohexanes, all fluorocyclohexanes except as noted above exhibit significant RSEs. This stems from the sizable RSE (*c*-1,1,2,2-$C_6H_8F_4$) = 9.2 kcal mol^{-1}, which in turn arises from an *E*(torsional term) = 10.0 kcal mol^{-1} in the energy decomposition, while [RSE (*c*-C_6H_{12}) + Δ] = 0.4 kcal mol^{-1} and *E*(angular term) = −1.2 kcal mol^{-1}. As above, the "adjacent CF_2" cyclohexanes exhibit the largest RSEs, topping out at RSE (*c*-C_6F_{12}) = 51 kcal mol^{-1}. While this seems large for the RSE of a cyclohexane, it is substantially smaller than values predicted by group equivalent reaction 1 (>80 kcal mol^{-1}).

RSEs of Chlorocyclohexanes *c*-$C_6H_xCl_{12-x}$. Chlorocyclohexanes exhibit RSEs between those for methyl- and fluorocyclohexanes, lying closer to those for fluorinated rings as was true for cyclopropanes and cyclobutanes. This aligns with electronegativity values. As above, a sizable *E*(torsional term) = 8.1 kcal mol^{-1} dominates RSE (*c*-1,1,2,2-$C_6H_8Cl_4$), with [RSE (*c*-C_6H_{12}) + Δ] = 0.9 kcal mol^{-1} and *E*(angular term) = −1.0 kcal mol^{-1}. The "adjacent CCl_2" cyclohexanes exhibit the largest RSEs, rising from RSE (*c*-1,1,2,2,3,3-$C_6H_6Cl_6$) = 15.0 kcal mol^{-1} to RSE (*c*-C_6Cl_{12}) = 44 kcal mol^{-1}. Since the C−Cl bonds are long, so the chlorides do not sterically protect the carbons well, this degree of strain suggests that perchlorocyclohexane should be susceptible to ring-opening reactions.

Why Some RSEs Are Larger than Expected for "Strain-Free" Cyclohexanes. Two observations noted above must be explained: first, that RSEs are larger than that of cyclohexane at all, given that the carbon atoms are nearly tetrahedral, and second, that RSEs are larger only in "adjacent CR_2" substituted cyclohexanes. Both can be interpreted as reflecting changes in bond distances upon substitution. In this regard, in our studies of RSEs of cyclopropanes and cyclobutanes,[17,18] it proved necessary to distinguish between geometric structural parameters and QTAIM structural parameters because of the highly distorted geometries around the ring carbons.[34,35] In the cyclohexanes, distortions are far smaller, and the geometric and QTAIM data differ insignificantly, so the distinction is unnecessary. We show both types of data in Table 5 to illustrate this, but for simplicity, we show only geometric data in Tables 6 and 7, and in the discussion, we use the term "distance data" to cover both data sets.[43] Bond path data for rings in Tables 6 and 7 are available as Supporting Information.

The distance data in Table 5 illustrate why the *c*-C_6R_{12} series contains more strain than cyclohexane or less substituted cyclohexanes. Compared are ring C−C distances for *c*-C_6R_{12} rings versus the more highly symmetrically substituted cyclohexanes free of adjacent CR_2 fragments; the latter are used to minimize the number of unique structural factors and to remove the "adjacent CR_2" factor. It is apparent that the dodecasubstituted rings are extremely crowded,[44] resulting in significantly elongated C−C ring bonds versus those in

Table 6. Ring $R_2C{-}CR_2$, $R_2C{-}CH_2$, and $H_2C{-}CH_2$ Geometric Bond Distances (MP2/6-311+G(d,p), Å) for "CR_2 Adjacent" Cyclohexanes[a]

		geometric bond distance		
	B	$R_2C{-}CR_2$	$R_2C{-}CH_2$	$H_2C{-}CH_2$
c-C_6H_{12}	0			1.532
c-C_6F_{12}	6	1.546		
c-1,1,2,2,3,3,4,4,5,5-$C_6H_2F_{10}$	4	1.543	1.516	
c-1,1,2,2,3,3,4,4-$C_6H_4F_8$	3	1.541	1.511	1.532
c-1,1,2,2,3,3-$C_6H_6F_6$	2	1.538	1.510	1.533
c-1,1,2,2,3,3,5,5-$C_6H_4F_8$	2	1.539	1.517	
c-1,1,2,2-$C_6H_8F_4$	1	1.532	1.510	1.534
c-1,1,2,2,4,4,5,5-$C_6H_4F_8$	1	1.538	1.516	
c-1,1,2,2,4,4-$C_6H_6F_6$	1	1.535	1.515	1.532
c-C_6Cl_{12}	6	1.590		
c-1,1,2,2,3,3,4,4,5,5-$C_6H_2Cl_{10}$	4	1.584	1.529	
c-1,1,2,2,3,3,4,4-$C_6H_4Cl_8$	3	1.583	1.522	1.523
c-1,1,2,2,3,3-$C_6H_6Cl_6$	2	1.575	1.527	1.526
c-1,1,2,2,3,3,5,5-$C_6H_4Cl_8$	2	1.571	1.529	
c-1,1,2,2-$C_6H_8Cl_4$	1	1.553	1.528	1.530
c-1,1,2,2,4,4,5,5-$C_6H_4Cl_8$	1	1.558	1.537	
c-1,1,2,2,4,4-$C_6H_6Cl_6$	1	1.553	1.529	1.527
c-C_6Me_{12}	6	1.593		
c-1,1,2,2,3,3,4,4,5,5-$C_6H_2Me_{10}$	4	1.591	1.533	
c-1,1,2,2,3,3,4,4-$C_6H_4Me_8$	3	1.591	1.536	1.520
c-1,1,2,2,3,3-$C_6H_6Me_6$	2	1.588	1.541	1.524
c-1,1,2,2,3,3,5,5-$C_6H_4Me_8$	2	1.584	1.539	
c-1,1,2,2-$C_6H_8Me_4$	1	1.567	1.545	1.529
c-1,1,2,2,4,4,5,5-$C_6H_4Me_8$	1	1.562	1.544	
c-1,1,2,2,4,4-$C_6H_6Me_6$	1	1.564	1.542	1.529

[a] Averages are given for cases where multiple examples of a bond type exist. "B" = number of contiguous ring $R_2C{-}CR_2$ bonds.

Table 7. Ring $R_2C\text{-}R_2C{-}CR_2\text{-}CR_2$, $R_2C\text{-}R_2C{-}CR_2\text{-}CH_2$, and $H_2C\text{-}R_2C{-}CR_2\text{-}CH_2$ Geometric Bond Distances (MP2/6-311+G(d,p), Å) for Octa-, Deca-, and Dodecasubstituted Cyclohexanes

	geometric bond distance	
	$R_2C\text{-}\mathbf{R_2C{-}CR_2}\text{-}CR_2$	$R_2C\text{-}\mathbf{R_2C{-}CR_2}\text{-}CH_2$
c-C_6F_{12}	1.546	
c-1,1,2,2,3,3,4,4,5,5-$C_6H_2F_{10}$	1.544	1.541
c-1,1,2,2,3,3,4,4-$C_6H_4F_8$	1.543	1.540
c-C_6Cl_{12}	1.590	
c-1,1,2,2,3,3,4,4,5,5-$C_6H_2Cl_{10}$	1.596	1.571
c-1,1,2,2,3,3,4,4-$C_6H_4Cl_8$	1.598	1.576
c-C_6Me_{12}	1.593	
c-1,1,2,2,3,3,4,4,5,5-$C_6H_2Me_{10}$	1.607	1.575
c-1,1,2,2,3,3,4,4-$C_6H_4Me_8$	1.612	1.581

cyclohexane.[45] In contrast, both the $R_2C{-}CH_2$ and $H_2C{-}CH_2$ distances in the less substituted rings are comparable to those in cyclohexane. It seems likely that the longer distances manifest themselves in greater ring strain. From the bond distance data overall, one predicts RSEs significantly larger than that of cyclohexane for the *c*-C_6R_{12} series and RSEs similar to that of cyclohexane for the *c*-1,1,3,3,5,5-$C_6H_6R_6$ and *c*-1,1,4,4-$C_6H_8R_4$ series. Put more generally, if substitution leads to an increase in the ring C−C distances, this will manifest as an increase in RSE. RSEs from the semi-homodesmotic approach are in accord with this.

One potential weakness in this analysis is that the C−C distance changes more on a percentage basis going from *c*-1,1,4,4-$C_6H_8Me_4$ to *c*-C_6Me_{12} than from *c*-1,1,4,4-$C_6H_8F_4$ to *c*-C_6F_{12}, yet the RSE trend is RSE (*c*-C_6F_{12}) > RSE (*c*-C_6Cl_{12}) > RSE (*c*-C_6Me_{12}). However, this must be viewed in the context of the preferred behavior of ring distances upon substitution. Substituting fluoride for hydrogen causes the $F_2C{-}CR_2$ ring distances to shrink versus the 1.532 Å $H_2C{-}CH_2$ distances in cyclohexane; for example, in *c*-1,1,4,4-$C_6H_8F_4$, they average 1.513 Å, while in *c*-1,1-$C_6H_{10}F_2$, they are even shorter (1.511 Å). Substituting chloride for hydrogen shrinks the ring bonds to a much smaller extent ($Cl_2C{-}CH_2$ distances are 1.530 Å in *c*-1,1,4,4-$C_6H_8Cl_4$ and 1.523 Å in *c*-1,1-$C_6H_{10}F_2$). In contrast, substituting methyl groups for hydrogen lengthens the $Me_2C{-}CH_2$ ring bonds, even for the meagerly substituted *c*-1,1-$C_6H_{10}Me_2$ (1.539 Å). These observations correlate with the electronegativity of the substituent and lead to a reasonable hypothesis regarding the RSE trend. The donating properties of methyl substituents "support" elongation of the ring bonds, while the withdrawing properties of fluoro/chloro substituents oppose it. Put another way, rings with fluoro/chloro substituents resist sterically induced area expansion[46] more than do rings with methyl substituents. So rings containing electron-withdrawing substituents have RSEs larger than those of identically substituted ones containing electron-donating substituents because the former rings prefer smaller ring distances but are forced by steric effects to have larger ones. The more electron-withdrawing the substituent is, the larger the resistance and so the RSE. The latter rings cope more easily with sterically forced ring area expansion because the donating nature of the substituents supports it.

Explaining the "adjacent CR_2" observation follows similar lines. Table 6 contains distance data for most of the rings not yet discussed, organized by the number of contiguous ring $R_2C{-}CR_2$ bonds, "B", present. A relationship between B and the $R_2C{-}CR_2$ distance is evident: as B decreases from 6 to 4/3 to 2 to 1, so does the distance.[47] Given the comments above, one expects that the RSEs should decrease, as well. To show this more explicitly, consider the progressively vicinally substituted series *c*-1,1,2,2-$C_6H_8Me_4$/*c*-1,1,2,2,3,3-$C_6H_6Me_6$/*c*-1,1,2,2,3,3,4,4-$C_6H_4Me_8$/*c*-1,1,2,2,3,3,4,4,5,5-$C_6H_2Me_{10}$/*c*-C_6Me_{12}. The corresponding $R_2C{-}CR_2$ distance (Å)/RSE (kcal mol^{-1}) data are 1.567/1.2, 1.588/2.9, 1.591/4.6, 1.591/6.3, and 1.593/11.9. While a correlation is clearly not linear, it clearly exists. A similar comparison holds when considering progressively vicinally fluoro- and chlorosubstituted rings.

It is worth noting what we believe is further evidence that fluorosubstituted rings resist bond length expansion so tenaciously that enforced expansions cause disproportionate increases in RSEs. In Table 7, we show expanded distance data for octa-, deca-, and dodecasubstituted cyclohexanes involving the types of $R_2C{-}CR_2$ bonds differentiated by fragments vicinal to them, that is, $R_2C\text{-}\mathbf{R_2C{-}CR_2}\text{-}CR_2$ (hereafter, a protected $R_2C{-}CR_2$ bond) versus $R_2C\text{-}\mathbf{R_2C{-}CR_2}\text{-}CH_2$ (an unprotected $R_2C{-}CR_2$ bond). One sees that protected $R_2C{-}CR_2$ bonds are always longer than unprotected ones, presumably because, from the perspective of the internal $R_2C{-}CR_2$ bond, the peripheral CR_2 fragments appear as larger substituents than do peripheral CH_2 fragments, and as stated, larger substituents force elongation of bonds. The differences are stark for the chloro- and methylsubstituted cyclohexanes, presumably a result of the steric bulk of the substituents.

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More importantly, note the similarity of the R_2C-$\mathbf{R_2C{-}CR_2}$-CR_2 distances for the fluorosubstituted cyclohexanes versus the sizable disparities for chloro- and methylsubstituted cyclohexanes. It is remarkable that the R_2C-$\mathbf{R_2C{-}CR_2}$-CR_2 distances are *longer* in the less substituted versions of the latter two than in the dodecasubstituted rings, contrasting with the general result that more substituents means longer bond distances. We attribute this to the lower symmetries of the less substituted rings giving a less symmetric electronic distribution, which is compensated for through-bond elongation. The salient point is that the fluorocyclohexanes do not exhibit this behavior, implying that these resist bond elongation tenaciously even when it might help in dealing with less symmetric electronic distributions. This in turn supports the idea that a fluorocyclohexane forced to elongate bonds to relieve steric interactions will exhibit a particularly large RSE as a reflection of this resistance.

CONCLUSIONS

The lore regarding cyclohexanes asserts that the near-tetrahedral geometries of the ring carbons dominate all else, so that RSEs will lie near zero. The results here indicate that this holds for modestly methylsubstituted cyclohexanes but is false for highly methylsubstituted and for most halosubstituted cyclohexanes. Indeed, RSEs can be sizable, even when the angular geometry around the ring carbons remains nearly tetrahedral. Large RSEs arise in cyclohexanes when C−C distances increase to accommodate substituent steric bulk. Electron-donating substituents support increased C−C distances to a degree, meaning RSEs increase only modestly with substitution, while electron-withdrawing substituents oppose increased C−C distances, meaning increases forced by steric demands result in substantial RSEs. We hope these observations will make their way into chemical education. Authors of organic chemistry books should clarify that, while cyclohexane is nearly strain-free, this is not true for substituted cyclohexanes. This could play into discussion of conformational choices for cyclohexanes beyond the classic example of *eq*-C_6H_{11}(*t*-Bu).

The semi-homodesmotic approach employed here seems unique in providing RSEs consistent with chemical intuition in two ways: they trend realistically, in tandem with ring carbon geometric distortions, and are not so large to be energetically untenable. We hope this work will spark interest in experimental thermodynamic studies of energetics, particularly, RSE energetics, of modestly and highly substituted cyclohexanes. We are unaware of any studies in this area, possibly because of the assumption that all cyclohexanes are "strain-free". Even if experiment cannot rigorously determine RSEs owing to their referential nature, knowledge of trends in estimated RSEs with substitution and with the electronic nature of the substituents would be useful and would help to determine whether the semi-homodesmotic approach truly outperforms homodesmotic methods. We noted previously[17] that a thermodynamic prediction of RSE (*c*-C_3F_6) was quite similar to that predicted by the semi-homodesmotic approach, and that this encouraged us to explore the approach further.

We would also welcome reaction studies aimed at exploiting large RSEs. For example, the large RSE of *c*-C_6Cl_6 (and the octa- and decasubstituted relations) suggests that it should be susceptible to ring-opening reactions. Such reactions would probably display reasonable kinetic behavior because the long C−Cl distances mean that the ring carbons are not well-protected from attacking substrates. A literature search did not provide any examples of ring-opening reactions of highly substituted chlorocyclohexanes; this seems like an area ripe for study.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01861.

> Graphics and tables showing details of the derivation of the semi-homodesmotic equations; optimized Cartesian coordinates (MP2/6-311+G(d,p) level) of all molecules examined; tables containing absolute energies from all models and molecules surveyed using homodesmotic reactions, and the RSEs determined from them; tables containing the CBS−QB3-derived semi-homodesmotic RSEs; analogues of Tables 6 and 7 using bond path data (PDF)

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Notes

The authors declare no competing financial interest.

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reference would contain both polar groups. Inspection of Table 1 shows that this never happens for the substituted cyclohexanes; reaction 4 always gives the *least* positive RSE.

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(41) See Supporting Information for details how reactions (a−k) cancel intramolecular interactions, how Δ is determined, and of what terms Δ is composed.

(42) As can be seen in the reactions in Figure 2, the nature of the semi-homodesmotic approach requires that RSE (*c*-1,1,3,3-$C_6H_8R_4$) = RSE (*c*-1,1,4,4-$C_6H_8R_4$), and RSE (*c*-1,1,2,2,3,3,5,5-$C_6H_4R_8$) = RSE (*c*-1,1,2,2,4,5,5,5-$C_6H_4R_8$).

(43) Another motivation for minimizing use of the bond path data is that extra critical points were found for *c*-C_6Cl_{12}, owing to its crowded structure. These do not affect the bond path data significantly but might clutter the discussion unnecessarily. See ref 44.

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(46) We use area expansion to distinguish between expansion of the ring owing to an increase in bond distance vs expansion by incorporation of another fragment into the ring.

(47) The only outlier from this relationship appears to be *c*-1,1,2,2,4,4,5,5-$C_6H_4F_8$, which has $F_2C{-}CF_2$, more in keeping with B = 2 than its actual B = 1. We believe this reflects the fact that the range of $R_2C{-}CR_2$ distances is far smaller for R = F than for R = Cl, Me, which in turn probably arises from the resistance of fluorosubstituted rings to the ring area expansion. However, another potential factor is that the CF_2 fragments may be slightly more repulsive in this molecule that in its B = 1 peers, leading to a slightly longer $F_2C{-}CF_2$ bond. As evidence, the QTAIM charges for the $F_2C{-}CF_2$ carbons are *q* = 1.15 for *c*-1,1,2,2,4,4,5,5-$C_6H_4F_8$, 1.14/1.12 for *c*-1,1,2,2,4,4-$C_6H_6F_6$, and 1.11 for *c*-1,1,2,2-$C_6H_8F_4$. These are obviously very small differences and may not be indicative, but they do follow the correct trend.