

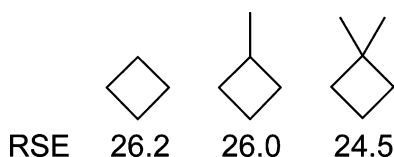
The *gem*-Dimethyl Effect Revisited

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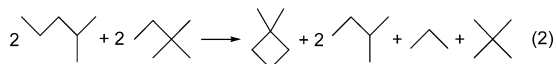
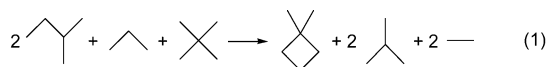
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Computation of the ring strain energy of 1,1-dimethylcyclobutane with a variety of methods reveals that there is no significant enthalpic component of the *gem*-dimethyl effect as measured by the ring strain energy.

Recently, Ringer and Magers reported computations suggesting a thermodynamic (enthalpic) component of the *gem*-dimethyl effect.¹ The greater facility of synthesis of small rings that have *gem*-dimethyl (or dialkyl) substitution over the unsubstituted case is called “the *gem*-dimethyl effect”. The effect was originally attributed to a kinetic effect caused by the substituents compressing the angle at that carbon, bringing the end groups closer together.² An alternative explanation attributes the increase to a greater number of *gauche* conformers (over the *anti* conformer) that leads to a greater concentration of species with the reactive ends closer together.^{2,3}

Ringer and Magers¹ estimated the conventional ring strain energy of cyclobutane (**1**), methylcyclobutane (**2**), and 1,1-dimethylcyclobutane (**3**) using isodesmic,⁴ homodesmotic,⁵ and hyperhomodesmotic⁶ reactions, by computing the electronic and zero-point vibrational energies with a variety of methods. The homodesmotic and hyperhomodesmotic reactions for 1,1-dimethylcyclobutane are shown as reactions 1 and 2. The ring strain energies (RSE) for the three cyclobutanes computed at B3LYP, MP2, and CCSD(T) are listed in Table 1.



For any given computational method, the homodesmotic and hyperhomodesmotic reactions give very similar RSE for the

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TABLE 1. Computed RSE of 1–3 (kcal mol⁻¹)

reaction	method	1	2	3
homodesmic	B3LYP ^{a,b}	23.15	21.50	18.88
	MP2 ^{a,b}	26.46	25.96	24.80
	CCSD(T) ^{b,c}	26.21	25.66	17.80
hyperhomodesmic	B3LYP ^{a,b}	23.07	19.64	16.31
	MP2 ^{a,b}	27.43	25.55	24.27
	CCSD(T) ^{b,c}	27.22	25.19	18.55
group equivalent	B3LYP ^{a,d}	23.15	21.54	20.91
	MP2 ^{a,d}	26.46	25.48	25.21
	CCSD(T) ^{e,d}	26.21	25.16	18.29
	G2MP2	25.83	25.60	24.46
	G3MP2B3	26.19	26.04	24.46
	PBE1PBE ^a	24.42	24.09	22.18
	MO5-2X ^e	26.93	26.07	24.89
protobranching	CCSD(T) ^f	26.74	26.61	24.91
	B3LYP ^{a,d}	19.12	18.68	21.42
	MP2 ^{a,d}	19.93	19.77	22.02
	CCSD(T) ^{e,d}	20.22	20.04	15.81
	G2MP2	19.71	20.29	21.78
	G3MP2B3	20.22	20.88	22.24
	PBE1PBE ^a	23.92	20.59	22.24
	MO5-2X ^e	20.82	20.94	23.10
	CCSD(T) ^f	20.27	21.06	22.71

^a 6-311+G(2df,2pd). ^b From ref 1. ^c CCSD(T)/6-311+G(2df,2pd)//MP2/6-311+G(2df,2pd) + ZPVE(MP2)/6-311+G(2df,2pd). ^d Using the values from ref 1. ^e 6-311+G(d,p). ^f CCSD(T)/6-311+G(2d,p)//PBE1PBE/6-311+G(2df,2pd) + ZPVE (PBE1PBE/6-311+G(2df,2pd)).

three cyclobutanes. Ringer and Magers were particularly focused on the trend in RSE as methyl groups are added to cyclobutane. At MP2, the RSE decreases with added methyl groups, but only by 3.2 kcal mol⁻¹ (hyperhomodesmotic). On the other hand, both B3LYP and CCSD(T) predict a much larger decrease. CCSD(T) using the hyperhomodesmotic reaction indicates that **2** is 2.0 kcal mol⁻¹ less strained than **1**. However, **3** is predicted to be dramatically less strained still: its RSE is 8.7 kcal mol⁻¹ less than that of **1**. The B3LYP values may be suspect, given the recent spate of papers describing significant problems inherent to most DFT methods and especially with B3LYP.^{7–11} Nonetheless, CCSD(T) is sometimes referred to as the “gold standard” of computational chemistry and so the significantly reduced RSE of **3** relative to both **1** and **2** was interpreted by Ringer and Magers¹ as indicative of an inherent enthalpic stability associated with *gem*-dimethyl substitution of strained rings.

We were particularly struck by the fact that the MP2 and CCSD(T) computed RSEs for **1** and **2** using either reaction are in excellent agreement. It is only for the RSE of **3** that the two methods disagree, by about 7 kcal mol⁻¹! Could these two methods agree in the RSEs of **1** and **2**, yet really be that far off in their predictions for **3**?

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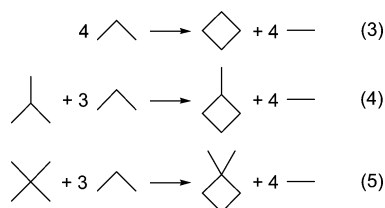
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We decided to investigate the RSEs of **1–3** using a variety of other computational methods. First, we chose to evaluate RSE using the group equivalent reaction.^{12,13} This reaction is homodesmotic along with preserving chemical groups as defined by Benson.¹⁴ It also has the advantage over the homodesmotic and hyperhomodesmotic reactions used by Ringer and Magers as involving smaller reference molecules.¹³ The group equivalent reactions for evaluating the RSEs of **1–3** are shown as reaction 3–5, respectively.



We first evaluated the RSE of **1–3** using the group equivalent reactions and the energies computed by Ringer and Magers at B3LYP, MP2, and CCSD(T).¹⁵ These RSEs are listed in Table 1, and differ by no more than 1 kcal mol⁻¹ from the values obtained with the hyperhomodesmotic reaction. Thus, the group equivalent reaction is effective in evaluating the RSEs of these compounds, and note the general insensitivity of the RSE to reaction type.

We next obtained the energies of all of the molecules present in reactions 3–5 with a variety of methods. The first are the composite methods G2MP2 (0 K)¹⁶ and G3MP2B3 (0 K).¹⁷ These are variants of the G2 and G3 methods that are parametrized to reproduce heats of formation to high accuracy. Both methods include a QCISD(T) energy computation. We also performed computations with two newer DFT methods that appear to perform better in producing isomerization energies.^{18,19} We optimized all structures at PBE1PBE/6-311+G(2df,2dp)²⁰ and at MO5-2X/6-311+G(d,p)²¹ and computed their zero-point vibrational energies (ZPVE). All computations were performed with GAUSSIAN-03,²² except the MO5-2X computations were performed with NWCHEM.²³ These estimated RSE are listed in Table 1.

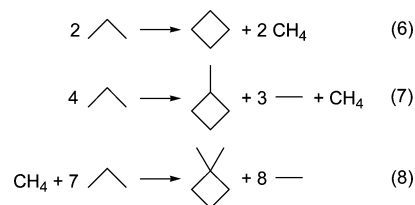
The PBE1PBE estimates for the RSE of **1–3** appear to be too small, though not as small as those predicted by B3LYP. The other methods (G2MP2, G3MP2B3, and MO5-2X) provide RSEs for **1** and **2** that are quite similar to those predicted by

MP2 and CCSD(T). If we exclude B3LYP and PBE1PBE, there is general excellent agreement between *all* of the variants described here for evaluating the RSE of these two compounds (the three different reactions and the six different computational methods). The average of these RSE estimates is 26.5 kcal mol⁻¹ for **1** and 25.6 kcal mol⁻¹ for **2**.

The RSE of **3** computed by using the group equivalent reaction and the CCSD(T) energies of Ringer and Magers is 18.29 kcal mol⁻¹, similar to the other CCSD(T) estimates. In contrast, G2MP2, G3MP2B3, and MO5-2X predict a much higher RSE of about 24.5 kcal mol⁻¹. These estimates are very similar to those obtained with MP2.

Given the discrepancy between our results for the RSE of **3** and Ringer and Magers CCSD(T) result, we attempted to reproduce their computations. Unfortunately, we lack sufficient disk space, but we were able to complete the computations at CCSD(T)/6-311+G(2d,p)//PBE1PBE/6-311+G(2df,2pd) with the PBE1PBE ZPVEs. The RSEs obtained with use of these CCSD(T) energies and the group equivalent reactions are listed in Table 1. Once again, we observe that these values are consistent with all of the computations *except* Ringer and Magers' CCSD(T) result.

Recently, Schleyer, Houk, and co-workers have presented an argument that 1,3-dialkyl interactions are stabilizing, the so-called protobranching effect.²⁴ Without getting sidetracked into whether the 1,3-dialkyl interactions are stabilizing or not, one can utilize a reaction that conserves the protobranches while having the products and reactants differ by the presence and absence of a ring. The "protobranching" reactions for evaluating the RSE of **1–3** are shown as reactions 6–8.



The RSEs obtained by using these protobranching reactions for **1–3** computed with the methods described above are listed in Table 1. The values of the RSEs predicted by the protobranching method are smaller than those predicted by the other reactions, due, as argued by Schleyer and Houk,²⁴ to nonconservation of the stabilizing protobranches in reactions 1–5. Our interest, however, is in the consistency of values produced by the different computational methods. Once again, we see very nice agreement among the different methods for the RSE of **1** and **2** using reactions 6 and 7. The outlier is once again the prediction for the RSE of **3** obtained with Ringer and Magers' CCSD(T) energies; it is 6–7 kcal mol⁻¹ smaller than the values obtained for the RSE of **3** with *all* of the other computational methods.

Another approach toward estimating the effect of *gem*-dimethyl substitution is to compare the preference for substitution of cyclobutane vs propane (reaction 9). (reaction 9 is equivalent to reaction 3 minus reaction 5.) The computed energies of reaction 9, evaluated with all of the methods, are listed in Table 2. As is clearly evident, all the methods provide values in a small range: 1.25 to 2.25 kcal mol⁻¹, except the

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

TABLE 2. Energy (kcal mol⁻¹) for Reaction 9^a

method	ΔE	method	ΔE
B3LYP	2.24	G3MP2B3	1.72
MP2	1.25	PBE1PBE	2.25
CCSD(T) ^b	7.92	MO5-2X	2.05
G2MP2	1.37	CCSD(T) ^c	1.83

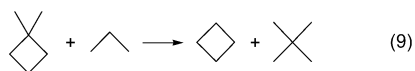
^a See Table 1 for definitions of the methods, which are listed in the same order. ^b Using Ringer and Magers CCSD(T) energies, see Table 1. ^c CCSD(T)/6-311+G(2d,p), see Table 1.

TABLE 3. Computed RSE of 4–6 (kcal mol⁻¹)

Method			
G2MP2	27.36	27.38	27.16
G3MP2B3	27.55	27.55	26.93

Method			
G2MP2	6.61	6.09	6.12
G3MP2B3	6.57	6.18	5.76

value of 7.92 kcal mol⁻¹ obtained with Ringer and Magers' CCSD(T) energies.

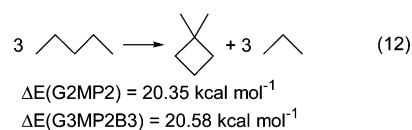
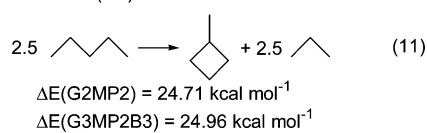


We therefore conclude that while the RSE decreases in the order **1** > **2** > **3**, the RSE of **3** is only a couple of kilocalories per mole less than that of **1**, not the 8 kcal mol⁻¹ suggested previously. We speculate that there is an error in Ringer and Magers' CCSD(T) computation of **3**.

If the *gem*-dimethyl effect had some significant enthalpic component, one should expect that the RSE of 1,1-dimethylcyclopropane would be smaller than that of methylcyclopropane and cyclopropane, and the same trend for the cyclopentanes. We have evaluated the RSE of these six molecules using the group equivalent reaction at G2MP2(0 K) and G3MP2B3(0 K) and report these values in Table 3. Once again, we observe that while the *gem*-dimethyl-substituted ring is less strained than the unsubstituted ring, the difference is very small, less than 1 kcal mol⁻¹.

gem-Dimethyl-substituted small rings are only slightly less strained (less than 2 kcal mol⁻¹) than their parent rings.

However, *gem*-dimethyl substitution is stabilizing relative to unbranched, linear alkanes. This point was made explicitly by Bach and Dmitrenko^{25,26} and is implicit in the idea of proto-branching²⁴ discussed by Schleyer and Houk. Bach used reaction 10 to estimate the strain energy of **3** relative to linear references as 21.9 kcal mol⁻¹. Using reactions 11 and 12, we similarly find that **2** and **3** are less strained when referenced against linear alkanes. This also means that using linear alkanes as the



reference, **3** is about 7 kcal mol⁻¹ less strained than **1**, implying that *gem*-substitution does stabilize the ring. This should be tempered by realizing that *neo*-pentane is about 5 kcal mol⁻¹ more stable than pentane. So, any enthalpic component to the *gem*-disubstitution manifests itself solely as the generic enthalpic preference of branched chains over linear chains. There is no enthalpic stabilization, by this we mean no reduction in ring strain energy, afforded to rings by *gem*-substitution. Thus, the “the *gem*-dimethyl effect”, in the context of favorable ring formation of the substituted over unsubstituted ring, has no significant enthalpic component.

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Supporting Information Available: Full citations for refs 22 and 23 and electronic energies and ZPVEs for all molecules. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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