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3 x Axial vs 3 x Equatorial: the $\Delta G_{\text{GA}}$ value is a robust computational measure of substituent steric effects

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KEYWORDS: Steric effects; linear free energy relationships; A-values; cone angles, solid angles.

**ABSTRACT:** We define $\Delta G_{\text{GA}}$ as the free energy change for the formal equilibrium: [13]G-H + 1-X-adamantane $\rightarrow$ [13]G-X + adamantane, where [13]G-H is the C_{12}H_{22} fragment of all-trans graphane with three-fold symmetry. This compares with a situation where the group X is equatorial to 3 cyclohexane rings with one where it is axial to 3 rings. $\Delta G_{\text{GA}}$ values vary from 2.9 (CN) to 145.7 kJ mol$^{-1}$ (CCl$_3$) and this wide range means that $\Delta G$ can be calculated with confidence. $\Delta G_{\text{GA}}$ values for Me, Et, i-Pr, and t-Bu form a regular series: 34.9, 63.3, 101.6 and 142.0 and clearly reflect the steric size of the groups. We propose a model where the six axial hydrogens surrounding X on [13]G-X provide a nearly circular constriction on the substituent close to its point of attachment, but which does not extend far above this. We compare these results with A-values and with calculations on 2- and 7-substituted [1(2,3)4]pentamantanes. We show that electronic effects on $\Delta G_{\text{GA}}$ values are negligible, but that they correlate well with computed cone and solid angles subtended by the substituent.

**Figure 1** (a) [13]G-CO$_2$Me with an electron density map for the six adjacent axial C-H groups, (b) Adamantane-1-CO$_2$Me.

We propose a single solution to these issues by changing the molecular scaffold from the two-fold symmetric center on a chair cyclohexane to the six-fold symmetric center of graphane (all-trans perhydro-graphene) which places X axial to three cyclohexane rings and so is surrounded by six axial hydrogens. In practice, we use the smallest symmetric fragment of graphane, [13]G$_3$ to give derivatives like [13]G-CO$_2$Me, Figure 1(a) which also shows the electron density associated with the six adjacent axial C-H groups superimposed: this provides a useful picture of how constriction of a substituent may operate. A natural foil to [13]G-X is the

**Introduction**

We describe a new computational approach to quantifying the steric effect of substituents in organic molecules. We recently highlighted$^1$ problems in rationalizing the steric ‘size’ of a substituent with respect to its effect on chemical reactivity and selectivity, showing how the apparently bulky pinacol boronic ester (BPin) can behave as a remarkably small substituent, depending on the reaction pathway being considered. We identified problems in computing existing parameters traditionally used in organic chemistry to define steric ‘size’ and, in particular, the A-value$^2$ which is based on the free energy difference, ($\Delta G$), between placing a substituent in an axial versus an equatorial position on cyclohexane in the chair conformation. Computation of the A-value of a substituent X requires calculation of the free energies of all conformers resulting from rotation around the C$_\gamma$-X bond (up to 3 for both axial and equatorial). With A-values typically lying in the range of 0-20 kJ mol$^{-1}$ and even the best quantum chemical methods only achieving accuracies of 3-4 kJ mol$^{-1}$ for conformer energy errors, there is clearly a large margin of error in such computational analyses.

![Equatorial to 3 rings](image1.png)

![Axial to 3 rings](image2.png)
C₃-symmetric bridgehead position on adamantane which places X equatorial to three cyclohexane rings, Figure 1(b), leading to formal equilibrium 1 shown below. These choices provide two important advantages (a) in almost all cases there is only one conformation each for [13]G-X and Adam-X thanks to the symmetry which simplifies interpretation of the results, and (b) we discovered that ΔGA values cover a range of >140 kJ mol⁻¹ with the consequence that good quantum chemical methods can provide a reliable scale of relative ΔG values (the reasons for the wide range will be discussed later).

No single parameter can reflect all aspects of steric effects; and the sterimol approach⁶ makes use of at least three parameters Bₛ, Bₛ, and L, to capture the shape and bulk of a group. We will show that ΔG values, while only a single parameter, do reflect the situation near the substituent's point of attachment, which will often be of chemical significance in studies of reaction rates and equilibria. For these cases, ΔG should provide a linear free energy relationship reflecting steric effects.

A wide range of 1-substituted adamantane derivatives are available, but very few [13]G-X are known,⁶ and synthesis is non-trivial, so eq.1 is likely to remain a purely computational tool. While we can compare results with those for the A-value equilibrium eq.2, it is vital therefore to show that ΔG values can be calculated reliably.

![Diagram](image)

**Experimental**

For eq. 1 and 2 we used both DFT and non-DFT calculational methods. DFT calculations were performed with ORCA 4.2.0⁷ using B3LYP DFT with the def2-TZVP basis set,⁷ in combination with Grimme’s D3BJ dispersion correction.⁸ Single-point domain-based local pair-natural orbital coupled cluster (DLPNO-CCSD(T))¹¹ calculations were then performed with the same basis set, combining these with the vibrational data from the DFT calculations to get a second values for ΔG. The DLPNO-CCSD(T) ΔG value thus provides a semi-independent check on the ΔG value from DFT and we find that the correlation coefficient for a plot of the DLPNO-CCSD(T) (non-DFT) ΔG value against the DFT value is 0.9991, indicating near perfect agreement. Over a range of >140 kJ mol⁻¹, the two methods only differed by more than 2 kJ mol⁻¹ for one case (CCl₃). For simplicity, in the rest of this paper we only quote the DFT values for ΔG but a table comparing the two methods is available in the Supporting Information. Entropy effects are small throughout for eq. 1. Conformational searches were carried out in Spartan¹² using the MMFF force field. Where more than one conformation was found for axial and equatorial cyclohexanes in eq. 2, a weighted average of the ΔG values for all axial vs all equatorial conformations is recorded as the calculated A-value, with both epimers of chiral conformations being counted separately. The threefold symmetry of [13]G-H and adamantane leads to conformational homogeneity for all but a few sp² hybridized substituents on [13]G (e.g., vinyl, CO₂Me) where there are two conformations, each with C₂ symmetry associated with 180° rotation of the group. Separate ΔG values are listed in Table 1 for these (i.e., conformational averaging has not been performed). The ΔG values for different rotamers are always very similar. While sp² hybridised groups show the usual 3-fold barrier, rotational barriers for sp² derivatives are very low (typically <1 kJ mol⁻¹).

**Results and Discussion**

Experimental A-values² and computed free energy values (ΔG in kJ mol⁻¹ at 298 K in the gas phase) for equations 1 and 2 and are shown in Table 1 which also includes values for equilibrium 3, discussed later. The calculations do a moderately good job of calculating A-values, although the correlation with experimental data is notably better for alkyl and related groups (correlation coefficient r² 0.97) where the range of values is ~20 kJ mol⁻¹ as compared with the selected functional groups (correlation coefficient 0.85) where the range of values is only ~4 kJ mol⁻¹.

**Table 1 Experimental and calculated A-values and ΔG (all in kJ mol⁻¹)**

<table>
<thead>
<tr>
<th></th>
<th>Exp A-value</th>
<th>Calc A-value</th>
<th>ΔGA, for eq. 1</th>
<th>ΔG for eq 3</th>
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<tbody>
<tr>
<td>Me</td>
<td>7.28</td>
<td>8.26</td>
<td>34.9</td>
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<tr>
<td>Et</td>
<td>7.49</td>
<td>10.0</td>
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<td>n-Pr</td>
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<tr>
<td>n-Bu</td>
<td>61.5</td>
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<td></td>
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<tr>
<td>i-Pr</td>
<td>9.25</td>
<td>9.3</td>
<td>101.6</td>
<td>141.6</td>
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<td>2-Bu</td>
<td>102.6</td>
<td></td>
<td>148.7</td>
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<tr>
<td>t-Bu</td>
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<td>23.9</td>
<td>142.0</td>
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<td>43.1, 44.1</td>
<td>53.2, 54.8</td>
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<td>45.6</td>
<td>41.6</td>
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<td>23.3</td>
<td>19.8</td>
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<td>NHMe</td>
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<td>49.4</td>
<td>53.4</td>
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<td>CN</td>
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<td>0.5</td>
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<td>NO₂</td>
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<td>4.9</td>
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<td>50.7</td>
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<td>3.1</td>
<td>33.7, 34.1</td>
<td>34.1, 35.5</td>
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<tr>
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<td>58.5</td>
<td>77.9, 80.1</td>
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<td>48.2, 49.2</td>
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<td>48.8, 48.9</td>
<td>63.4, 65.1</td>
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**Table 1**

<table>
<thead>
<tr>
<th>Substituent</th>
<th>ΔG (kJ mol⁻¹)</th>
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<tr>
<td>B gly</td>
<td>3.05</td>
</tr>
<tr>
<td>B pin</td>
<td>1.75</td>
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</tbody>
</table>

*Only the all-anti conformation of these substituents were calculated.*

**1,3,2-Dioxaboranyl**

The relative ΔG values for eq. 1 carry the most interesting information for chemists. It is well-known that the A-values for Me, Et, i-Pr and t-Bu do not reflect the steric size of these substituents because Et and i-Pr, when in an axial position, can rotate to avoid interacting much with the axial hydrogen atoms on the cyclohexane ring. The ΔG values (34.9, 63.6, 101.6 and 142.0) are clearly much closer to representing the relative size of the groups correctly because rotation around the Adam-X and [13]G-X bonds is irrelevant. Et, n-Pr, and n-Bu groups have very similar ΔG values (63.3, 61.9 and 61.5) while the i-Pr and 2-butyl [CH(CH₃)₂CH₃] groups are also very similar (101.6 and 102.6), showing that the more distant atoms of a substituent are beyond the range of the constriction. We note that carbonyl substituents have larger ΔG values than their A-values might suggest, when compared with simple alkyl groups. Thus, CO·Me has a larger ΔG value than methyl, although its A-value is appreciably smaller. When axial on cyclohexene, the carboxymethyl group can rotate to interact only slightly with the axial hydrogen atoms. We find that Bpin and B gly have ΔG values of 20.6 and 19.6, respectively, barely half that for CO·Me (37.8) and in line with their small A-values determined experimentally.

Figure 2(a) below shows the 90% electron density surface for the six C-H groups of [13]G-H viewed from above, generated by Spartan using B3LYP/def2-TZVP DFT. This ring of axial hydrogen atoms is close to exerting a circular constricting force on the substituent. Contrast this with the very lop-sided force that two axial hydrogen atoms on an axially-substituted cyclohexane exert on the substituent. This is surely the reason why ΔG values provide an improved picture of the steric size of substituents. Not that a circle of eight He atoms has been used in the development of ligand knowledge bases for monodentate P-donor ligands.

![Figure 2](image-url)

**Figure 2** (a) 90% electron density surface for six C-H groups, (b) Space-filling model of t-Bu-C≡C-[13]G (from Spartan).

The alternative view of the electron density surface for the six C-H groups in Figure 1(a) hints that the constriction does not extend very far above the general plane of [13]G. We estimate that the effect is small beyond ~2 Å above the point of attachment (a similar limit must also apply to A-values). To illustrate this point, we calculated a very small ΔG of 2.61 for the t-Bu-C≡C- substituent (see Figure 2(b)), compared with 142.0 for t-Bu itself. The smaller value for t-Bu-C≡C- than for H-C≡C- (7.94) may be real and due to attractive London dispersion forces between t-Bu and [13]G-H.

![Figure 3](image-url)

**Figure 3** (a) Flexing of axial-substituted cyclohexane, (b) plane defined by the 3 outer carbon atoms of [13]G-X, (c) [22]G-Me.

A striking aspect of Table 1 is that the energetic cost (ΔG) of placing a bulky group on [13]G is much greater than the A-value. The range of ΔG values (>140 kJ mol⁻¹) is approximately seven times that for A-values. It might be expected that the range would be nearer three times, since there are six axial hydrogen atoms on [13]G to interact with the substituent, compared with two in an axial cyclohexane. However, the main geometrical change when X is axial on cyclohexane is that it flexes away from the ring as indicated in Figure 3(a) above and this cannot of course be productive for [13]G-X. More costly ways of relieving strain must come into play and examination of the structure of, e.g., [13]G-t-Bu, shows that the C-X bond lengths to 1.64 Å, but also that the central carbon of [13]G moves upward with the substituent – the whole structure begins to dome upwards. This can be assessed by measuring the height of the central carbon above a plane through the three outer carbon atoms of the [13]G derivative, as shown in Figure 3(b). The differential height (height above the plane for [13]G-X minus the height for [13]G-H itself) is 0.22 Å for the methyl derivative rising to 0.39 Å for [13]G-t-Bu. The energy cost of these distortions was assessed with B3LYP/def2-TZVP/3DBJ calculations. Distorting [13]G-H to the geometry of the t-Bu derivative costs 73.8 kJ mol⁻¹. Distorting 2-methylpropane to its geometry in [13]G-t-Bu costs 23.8 kJ mol⁻¹. The larger fragment may carry the larger cost, but this in no way invalidates assigning ΔG values as substituent effects. Stretching a C-C bond in 2,2-dimethylpropane from its equilibrium value to 1.64 Å costs 11.8 kJ mol⁻¹. The large energies associated with eq. 1 are clearly the sum of these changes in addition to the expected van der Waals interactions and other changes.

Would the doming affect a larger area in an all-trans graphene derivative? This was tested by running calculations on the next larger C₃-symmetric derivatives, for example [22]G-Me as shown in Figure 3(c) above. The calculated energy difference for [22]G-Me vs 1-methyladamantane is very similar to that for the [13]G-Me case (32.5 vs 32.8 kJ mol⁻¹) but there is an increase for the corresponding t-Bu-derivatives (153.6 vs 141.5) - note that these values differ from those in Table 1 because it was necessary to use the smaller def2-svp(b) basis set for these calculations. The doming clearly spreads further for the [22]G derivatives,
but the increase is not large, so it appears that the [13]G system captures most of the doming effect.

A remarkable experimental study\textsuperscript{15} has shown that [1(2,3)4]pentamantane (or T\textsubscript{P}-pentamantane) can be converted, in surprisingly good yields, to pentamantane-2-Br by one method and to pentamantane-7-OH by another. Other derivatives can then be made by substitution.

Equilibrium 3 is therefore potentially experimentally accessible so should this be used instead of eq. 1 to give a diamondoid perspective on steric effects? Pentamantane is extremely rigid, and the doming seen above is not possible. The substituent-bearing carbon does move up when a large substituent is attached to the hindered 2-position, but other carbons in the structure barely move at all. The other geometrical change that is noticeable is that bond lengths to the substituents are stretched significantly. In pentamantane-2-tBu, this bond length is 1.69 Å. These severely localized strain effects are surely the cause of the generally greater \( \Delta G \) values for eq. 3 compared to eq.1 (~13 times \( \Delta A \)-values). We find that the correlation between eq. 1 and eq. 3 for the substituents in Table 1 is very good, \( r^2 = 0.95 \), which is surely reassuring for the general use of these values. However, six small substituents have lower \( \Delta G \) values for eq. 3 than for eq. 1: F, Cl, OH, NH\textsubscript{2}, CN and ethynyl which is unexpected. We have traced this to the use of the smaller def2-SV(P) basis set for the DFT calculations on the large pentamantane molecule (C\textsubscript{56}H\textsubscript{42}); see the Supporting Information for details. There are therefore problems with eq. 3 and, while it is conceptually simpler than eq. 1, we believe that eq. 1 will prove more generally useful. Pentamantane is also much more rigid than most organic molecules, so eq. 1 is probably more useful for comparisons.

If the \( \Delta G \) values from eq. 1 are to be used as measures of steric effects, it is desirable to confirm that they do not incorporate electronic effects. All the bonds close to the point of substitution in adamantane and [13]G only differ in stereochemistry, so it is reasonable to expect electronic effects to be small. To check on this, we sought other evidence by plotting \( \Delta G \) against Hammett \( \sigma_m \) values, traditional measures of electronic effects (resonance effects are not to be expected). Reliable values exist\textsuperscript{16} for \( \sigma_m \) for all the substituents in Table 1, and a plot of \( \Delta G \) vs. \( \sigma_m \) (see the Supporting Information) shows no obvious trends and with \( r^2 = 0.09 \), essentially no correlation. The best that can be said from this is that we see no positive evidence for electronic effects.

We also sought correlation with the best known steric linear free energy relation: the Taft-Dubois \( E'_s \), steric parameter,\textsuperscript{17} which is based on the acid catalysed esterification of carboxylic acids in MeOH at 40 °C. \( E'_s \) values only exist for 14 of the groups in Table 1. A plot of this data (Figure 4) against \( \Delta G \) leads to a poor correlation (\( r^2 = 0.33 \)) but vinyl (2.07) and phenyl (2.31) highlighted in red, the only unsaturated groups, are clearly out of line with the rest. If these two points are removed, we then get \( \Delta G = 0.013 \ E'_s - 0.40 \), with \( r^2 = 0.83 \), which is satisfactory. The Taft-Dubois \( E'_s \) values for vinyl and phenyl are larger than for t-Bu which is unlikely if they only reflect steric size, so we believe the problem lies with the \( E'_s \) values, not the \( \Delta G \) values. We have suggested that eq. 1 gives a consistent picture of substituent size as if viewed by an eye placed at the point of attachment. Cone angles\textsuperscript{18} and solid angles\textsuperscript{19} often used by inorganic chemists to quantify the steric effects of ligands, are based on a closely related view, as shown in Figure 5 below.

**Figure 4** \( \Delta G \) vs Taft-Dubois \( E'_s \)

**Figure 5** Cone and solid angles; see the text for descriptions.

The substituent cone angle \( \theta \) is the apical angle of a cone with its apex at the point of attachment which just touches the van der Waals surface of the substituent. In Tolman’s original approach,\textsuperscript{18a} the ligand considered was modified to the smallest possible cone angle, whereas later approaches allowed for some structural relaxation,\textsuperscript{18c,d} making data selection potentially more challenging. The substituent solid
angle $\Omega$ can be visualized as follows: the point of attachment of the substituent is replaced with a light source so that the substituent casts a shadow on a sphere surrounding the molecule. The value of the solid angle (in steradians) is numerically equal to the size of that shadowed area divided by the squared radius of the sphere. Substituent solid angles therefore reflect the shape of the group viewed in this way and, in principle, offer an improved view of substituent size relative to cone angles, as well as reducing the impact of conformational freedom.\textsuperscript{18c}

Cone and solid angles are purely geometrical parameters so if good correlations of these with $\Delta G$ values are found, this would provide further evidence that eq. 1 is not skewed by electronic effects. Allen and co-workers\textsuperscript{20} have provided procedures, written in Mathematica,\textsuperscript{21} for the calculation of exact cone and solid angles. They were concerned with the steric sizes of phosphine ligands coordinated to Fe and other transition metals and they set a metal-to-ligand distance of 2.28 Å. We tried to use a more realistic bond distance for our substituents, but found that at any distance below 1.9 Å, the calculations failed. We were therefore forced to use the 2.28 Å distance, so our values are, at best, only proportional to the true values. A full set of values for $\theta$ and $\Omega$ for both Adam-X and [13G]-X is listed in the Supporting Information. For $\Omega(S)$, the relationship is $\Omega(S)_{[13G]-X} = 0.90\Omega(S)_{\text{Adam-X}} + 0.15$, $r^2 = 0.99$. This means that larger substituents like t-Bu have their solid angles compressed by a factor of ~0.90 relative to small groups when on the [13G] skeleton, which reflects the effects of the constriction. We will only use the Adam-X values for the remainder of this discussion.

The correlations of cone and solid angles with $\Delta G$ are quite poor: $r^2 = 0.66$ and 0.41 respectively but we noted that, for the solid angle plot, this was clearly caused by outlier values for Br (14.8) and SiMe$_3$ (80.5), highlighted in green in Figure 6 below. For these groups it is likely that the main bulk lies well above the reach of the ring fence of hydrogens.

**Figure 6** Solid angle vs $\Delta G_{\text{CA}}$ (key: alkyl groups (blue), other sp$^3$ substituents (red), sp$^2$/sp substituents (black) and Br/SiMe$_3$ outliers (green))

When the points for Br and SiMe$_3$ are removed, the plot of $\Delta G$ vs $\Omega(S)$ yields a much-improved correlation: $\Delta G = 139\Omega(S) - 203$; $r^2 = 0.86$ (the cone angle plot improves to $r^2 = 0.76$). There is little sign of deviations that might be due to electronic effects in $\Delta G$ and hybridization appears to have a minimal effect. Thus, plots for sp$^3$-hybridized groups (blue and red in Figure 6): $\Delta G = 137\Omega(S) - 193, r^2 = 0.94$, and sp$^2$-hybridized substituents: $\Delta G = 129\Omega(S) - 186, r^2 = 0.78$, have similar slopes. Note that a plot for the three halogens gives: $\Delta G = 2.75\Omega(S) + 8.1, r^2 = 0.75$; the greatly reduced slope probably shows that the steric bulk of the larger halogens is moving out of range of the constriction. A recent paper\textsuperscript{22} has shown that attractive London dispersion forces make a significant contribution to the small $A$-values for the larger halogens. We calculated that the $\Delta G$ value for Br would be 28.5 in the absence of dispersion. The $\Delta G$ value for Me/Si would be 105.7, so this could be a more general effect. The effect of dispersion in making the $\Delta G$ value for the t-BuC≡C- group so small has already been noted.

**Conclusion**

We believe that $\Delta G$ values are valuable new parameters for the assessment of the steric 'size' of substituents. They arise from a readily understood source: the near circular constriction force on the substituent in [13G]-X from the six adjacent axial hydrogen atoms. The wide range of $\Delta G$ values (~150 kJ mol$^{-1}$ cf <20 kJ mol$^{-1}$ for $A$-values for substituents in this study) and the reduced conformational space of these systems and means that these can be calculated with confidence and interpreted more easily. While no one parameter can ever describe the steric effect of a substituent in all circumstances and from all angles, the $\Delta G$ values from formal equilibrium 1 provide a clear picture of the steric size of a group close to its point of attachment, often a chemically valuable viewpoint in mechanistic studies of organic molecules. We show that $\Delta G$ values lack any correlation with Hammett $\sigma_m$ values and so do not appear to be contaminated by electronic effects, and this is backed up by correlation of $\Delta G$ values with the purely geometrical data of cone and solid angles.

**ASSOCIATED CONTENT**

**Supporting Information.** Tabulation of both B3LYP/def2-TZVP/D3BJ and DLPNO-CCSD(T)/def2-TZVP $\Delta G$ values for all substituents. Details of the computational problems encountered with eq. 3. Correlation of $\Delta G$ values with Hammett $\sigma_m$. Table of cone and solid angles vs $\Delta G_{\text{CA}}$, including values for both Adam-X and [13G]-X derivatives. This material is available free of charge via the Internet at http://pubs.acs.org. Full listings of xyz geometries and computational output for all calculations have been deposited at

**AUTHOR INFORMATION**

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REFERENCES


3. (a) The [13]G nomenclature was first used by A. A. Fokin, D. Gerbig, and Peter R. Schreiner, σ/σ- and π/π-Interactions Are Equally Important: Multilayered Graphanes, J. Am. Chem. Soc. 2011, 133, 20036–20039; (b) the systematic name for [13]G-COOMe is based on aromatic hydrocarbon phenalene: methyl (3as,6as,9as)-dodecahydro-3aH-phenalene-3a-carboxylate.

4. For a recent review that covers other ways of assessing steric size, including solid and cone angles, with a particular focus on ligands in organometallic chemistry see: D. J. Durand and N. Fey, Computational Ligand Descriptors for Catalyst Design, Chem. Rev. 2019, 119, 6561–6594.


