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EPR Data Do Not Indicate That Hyperconjugation Stabilizes Alkyl Radicals

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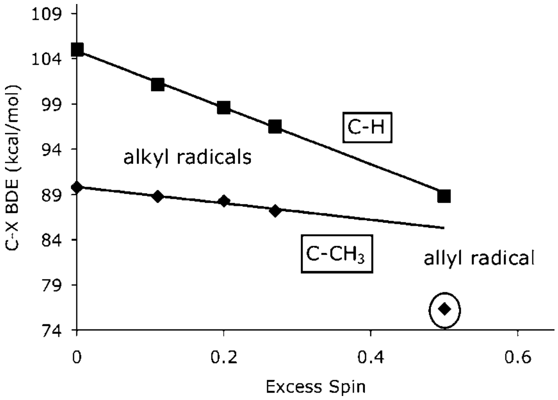
ABSTRACT



Ingold and DiLabio recently proposed that a correlation between C–H bond dissociation energies (BDE's) and spin delocalization terms calculated from EPR spectra was evidence that hyperconjugation plays an important role in stabilizing alkyl radicals. This correlation cannot be extended to C–C BDE's and the nature of the deviation is inconsistent with modern data on the 1,3 carbon–carbon interaction energies in alkanes. This result suggests that hyperconjugation is not a key factor in determining BDE's.

Recently in this journal, Ingold and DiLabio asserted that the spin delocalization observed in the EPR spectra of alkyl radicals was evidence that hyperconjugation is an important factor in determining alkane C−H bond dissociation energies (BDE's).[1] This claim was based on the good linear correlation between the C−H bond dissociation energies and the estimated excess spin on β-methyl groups in alkyl radicals. Although compelling at first glance, the argument breaks down when applied to other types of bonds. The failure of the Ingold/DiLabio analysis is that it does not take into account that a bond dissociation energy is a two-state problem and therefore the effect of substituents on the *reactants and products* must be evaluated.

It has been recognized for many years that the effects of α-alkyl substituents on C−X BDE's are highly dependent on the nature of X (eq 1).[2,3] Even the seemingly subtle

$$(CH_3)_nH_{3-n}C{-}X \rightarrow (CH_3)_nH_{3-n}C\bullet + X\bullet \qquad (1)$$

transition from X = H to X = CH_3 causes a marked change in the substituent effect. This point has been highlighted in several recent papers[4−6] and it has been shown that the need

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(1) Ingold, K. U.; DiLabio, G. A. *Org. Lett.* **2006**, *8*, 5923.

(2) Rüchardt, C. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 830.

(3) Nicholas, A. M. d. P.; Arnold, D. R. *Can. J. Chem.* **1984**, *62*, 1850.

(4) Matsunaga, N.; Rogers, D. W.; Zavitsas, A. A. *J. Org. Chem.* **2003**, *68*, 3158.

(5) Zavitsas, A. A. *J. Chem. Educ.* **2001**, *78*, 417.

(6) Coote, M. L.; Pross, A.; Radom, L. *Org. Lett.* **2003**, *5*, 4689.

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to simultaneously explain trends in C−H and C−C bonds puts significant constraints on any explanation of the α-alkyl substituent effect.[7] Nonetheless, this point has not been fully appreciated by the entire organic chemistry community. In this Letter, the problems in the Ingold/DiLabio analysis of BDE's are identified and critical criteria for any analysis of this substituent effect trend are presented.

The Ingold/DiLabio analysis[1] begins by using hyperfine coupling constants from the EPR spectra of alkyl radicals to calculate excess spin densities on the β-methyl groups of the ethyl, isopropyl, and *tert*-butyl radicals. From there, they split out the portion that they believe is from spin-polarization and assign the rest to hyperconjugation. Given the regular nature of BDE substituent trends, it is not surprising that their estimated excess spin term correlates with the C−H BDE's (Figure 1). In fact, their term for the spin-polarization (i.e., non-hyperconjugation component) also gives a good correlation with the C−H BDE's. The final step in their analysis was to note that when extrapolated out to an excess spin density of 0.5, the correlation line nearly passes through a point appropriate for the allyl radical.[8] From this result, they concluded that the bond weakening observed in methyl-substituted C−H bonds is caused by the same factor that weakens the methyl C−H bond in propene, namely electron delocalization.

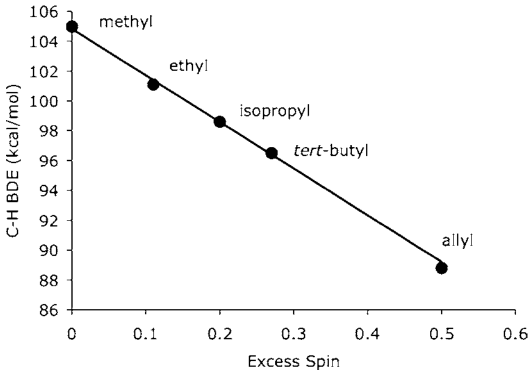

Figure 1. Plot of C−H BDE's vs the excess spin density that Ingold and DiLabio attributed to hyperconjugation. The correlation line is based on only the alkyl radicals. The excess spin density on the allyl radical is set at 0.5.

However, if one attempts the same analysis with C−CH_3, C−OH, C−SH, or C−I bonds, a completely different conclusion is suggested; the extrapolated lines do not come close to the BDE of the allyl systems despite the fact that the same alkyl radicals are formed with presumably the same stabilization from hyperconjugation (Figure 2).[9] The divergences for the allyl radical range from 8.9 to 20.4 kcal/mol. The reason for the discrepancies is well-known and documented. Methyl substitution affects the relative stability of *both the parent species and the resulting alkyl radical.*[2−6] The Ingold/DiLabio analysis requires that the C−H BDE be the unique measure of alkyl radical stability whereas all other BDE's are tainted by other effects and therefore are unsuitable. Does this leap of faith have any theoretical support?

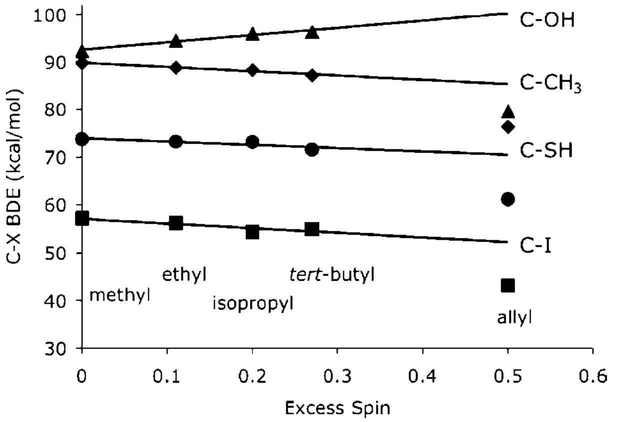

Figure 2. Plot of C−OH (triangles), C−CH_3 (diamonds), C−SH (circles), and C−I (squares) BDE's vs the excess spin density that Ingold and DiLabio attributed to hyperconjugation. The correlation lines are based only on the alkyl systems. The excess spin density on the allyl radical is set at 0.5.

It is clear that the polarity of bonds has a strong influence on C−X BDE's. Data for C−OH bonds clearly indicate that methyl substituents provide greater stabilization to the alcohol than the radical and therefore strengthen the bond. This effect has been documented before and is undoubtedly due to the C−O bond polarity and ability of the methyl group to stabilize the resulting partial positive charge on the α-carbon.[4−6] If one wishes to eliminate the effects of bond polarity in an analysis, the obvious choice is C−CH_3 bonds because the C−H bond has a small, but significant polarity $(C^{\delta-}-H^{\delta+})$.[10] However, C−$CH_3$ BDE's do not support the Ingold/DiLabio analysis and by their logic, suggest that hyperconjugation has a minor effect on the stability of alkyl radicals. The C−SH and C−I bonds were included in Figure 2 because the electronegativities of sulfur and iodine are close to that of carbon. These bonds give nearly the same pattern as the C−CH_3 bonds. The data in Figures 1 and 2 indicate that the pattern observed in C−H BDE's is unique and not at all representative of other trends in carbon BDE's.

Ingold and DiLabio do not explicitly state why they chose C−H BDE's for their analysis. In a footnote, they indicate that they assumed that the C−CH_3 BDE's would be affected

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(7) Gronert, S. *J. Org. Chem.* **2006**, *71*, 7045.

(8) The plot in Figure 1 is slightly different than that presented by Ingold and DiLabio. Here, BDE's from Blanksby and Ellison have been used (see ref 9). Ingold and DiLabio do not state the origin of their BDE's. The values for the alkanes match those of Blanksby and Ellison, but the value for propene that they used differs by nearly 3 kcal/mol from the Blanksby and Ellison value. The important effect is that now the 32%/62% spin polarization/hyperconjugation model in Figure 1 of the Ingold/DiLabio paper gives a better fit than the proposed 45%/55% model.

(9) Bond energies taken from: Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res.* **2003**, *36*, 255.

(10) Lazzeretti, P.; Zanasi, R.; Raynes, W. T. *J. Chem. Phys.* **1987**, *87*, 1681.

by 1,3 carbon−carbon interactions that would mask the impact of hyperconjugation. To explain the deviation seen in Figure 2 (i.e., the correlation line passes above allyl), one must assume that the 1,3 carbon−carbon interactions are attractive and therefore strengthen C−C bonds. Ingold and DiLabio appear to have adopted this assumption and state "1,3-methyl/methyl interactions have conveniently been viewed as attractive..." *Although this assumption has persisted in textbooks, decades of data indicate that it is false.* Nearly 75 years ago, Eyring[11] first realized that the 1,3 distances in these systems are shorter than the combined van der Waals radii and suggested that variations in C−H BDE's are related to changes in 1,3 repulsive interactions. This appears to be the original explanation for the fundamental trend observed in alkane BDE's. About 25 years later, Bartell provided spectroscopic data that indicated that 1,3 interactions are indeed repulsive.[12−15] This was followed by a set of compelling papers from Rüchardt in the 70's and 80's that reached a similar conclusion.[2,16−18] At about the same time, Bauld used computational methods to estimate the magnitude of repulsive 1,3 methyl−methyl interactions (~8 kcal/mol)[19] and Wiberg used repulsive 1,3 interactions to explain features of small-ring chemistry.[20] Gillespie has incorporated this idea into his ligand close-packing (LCP) theory.[21,22] In the past year, this lab used computations on model systems to show that nonbonded 1,3 interactions are repulsive.[7] Finally, Ziegler very recently used a DFT energy partitioning scheme to show that the 1,3 interaction terms are repulsive in alkanes and that radical stabilization has little influence on the observed trends in C−H BDE's.[23] *In these studies, it is especially noteworthy that completely different methodologies have led to similar estimates of the magnitude of 1,3 repulsive interactions in alkanes*. There is no doubt that the present literature solidly supports the conclusion that 1,3 interactions are repulsive. Although it may have been convenient to explain the trends in alkane heats of formation on the basis of attractive 1,3 interactions, modern data indicate that this is a false assumption. In short, any claims that 1,3 carbon−carbon interactions are attractive need to refute a broad set of data gathered over many years in several unallied labs.[24]

It is true that Wodrich and Schleyer[25] recently developed an additivity scheme that allowed them to efficiently fit the heats of formation of alkanes and alkyl radicals with a model based on attractive 1,3 carbon−carbon interactions. Their work also shows that this is not a unique fit and that models based on repulsive 1,3 interactions provide good fits to the same data. However, this paper provides no information on the physics of the 1,3 interactions; it only explores the variety of fitting schemes that can be used to reproduce alkane and alkyl radical heats of formation. Many others have undertaken the same exercise over the years and as early as 1965, 25 different schemes, with various assumptions about 1,3 interactions, had been presented.[26]

The notion that 1,3 interactions are stabilizing seems to trace back to Pitzer and Catalano, who were able to reproduce the heats of formation of alkanes using a model based on attractive van der Waals interactions.[27] In that model, the repulsive portion of the Lennard-Jones potential was arbitrarily neglected and therefore all nonbonded interactions were forced to be attractive. This led to a good fit for all-anti alkanes, but the model incorrectly predicted that gauche conformers would be more stable than anti conformers (their model treats all steric interactions as stabilizing). Although there is no theoretical foundation for this model, it gained wide acceptance, apparently because it offered an expedient means of explaining the effect of branching on the heats of formation of alkanes. As noted above, however, it is inconsistent with available experimental and computational data on 1,3-interactions.

In addition, the Ingold/DiLabio analysis is based on a second, unsupported assumption. They believed that the stabilization gained by electron delocalization would be independent of the nature of the orbital interaction. With this logic, 0.5 electron of spin delocalization via hyperconjugation to C−H bonds in the alkyl radicals would provide the same stabilization as the π-resonance in the allyl radical. This is unlikely and would be a surprising coincidence. In one case, electron donation to the radical center would occur from a low-energy, C−H σ-orbital via an awkward 3-center geometry with compromised π-overlap (Figure 3). In the other, donation occurs via a perfect π-interaction with a π-bond whose energy better matches that of the radical center (similar issues are at play in interactions with the corresponding σ* and π* orbitals in these systems). There is no reason to expect equivalent efficiencies of stabilization under these conditions. For example, C−C σ and π bonds have similar levels of electron "delocalization" (i.e., bonding electrons are fully shared), but have very different bond energies due to differences in orbital overlap. It therefore would be a surprise for the allyl radical to fit the same correlation line as the alkyl radicals even if hyperconjugation

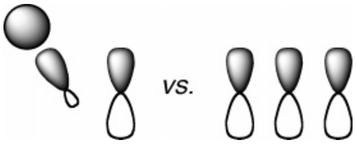

Figure 3. Comparison of interactions involved in the delocalization observed in alkyl and allyl radicals.

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[11] Eyring, H. *J. Am. Chem. Soc.* **1932**, *54*, 3191.
[12] Bartell, L. S.; Kuchitsu, K. *J. Chem. Phys.* **1962**, *37*, 691.
[13] Fitzwater, S.; Bartell, L. S. *J. Am. Chem. Soc.* **1976**, *98*, 5107.
[14] Bartell, L. S. *Spectrochim. Acta Part A* **2005**, *61*, 1283.
[15] McKean, D. C. *Chem. Soc. Rev.* **1978**, *7*, 399.
[16] Rüchardt, C.; Beckhaus, H.-D. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 429.
[17] Rüchardt, C.; Beckhaus, H.-D. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 592.
[18] Brocks, J.; Beckhaus, H.-D.; Beckwith, A. L. J.; Rüchardt, C. *J. Org. Chem.* **1998**, *63*, 1935.
[19] Bauld, N. L.; Cessac, J.; Holloway, R. L. *J. Am. Chem. Soc.* **1977**, *99*, 8140.
[20] Wiberg, K. B. *Angew. Chem.* **1986**, *98*, 312.
[21] Gillespie, R. J.; Robinson, E. A. *C. R. Chim.* **2005**, *8*, 1631.
[22] Gillespie, R. J.; Robinson, E. A. *Chem. Soc. Rev.* **2005**, *34*, 396.
[23] Mitoraj, M.; Zhu, H. J.; Michalak, A.; Ziegler, T. *J. Org. Chem.* **2006**, *71*, 9208.

were the dominant effect. Ingold and DiLabio argue that delocalization is stabilizing, but this is not really accurate for neutral species; it is the bonding that results from delocalization that leads to the stabilization. The EPR data are clear evidence of spin exchange related to hyperconjugation, but this could occur with little or no stabilization of the radical center. Ingold and DiLabio's effort to parametrize the energetic impact of hyperconjugation on the basis of the π-resonance energy in the allyl radical has no theoretical foundation, but is the crux of their argument.

When analyzing BDE data, it is always a challenge to link straight-line correlations to the energetics of a specific physical interaction. In this case, a good correlation between spin delocalization and C−H bond dissociation energies was used as evidence of hyperconjugative stabilization in alkyl radicals.[28] It is evidence of hyperconjugation (i.e., some level of interaction between the radical and C−H bonding orbital), but the authors used unsupported assumptions to link the hyperconjugation to the observed differences in BDE's. Because of regular trends in BDE's, as well as autocorrelation between many structural/electronic features in alkanes/alkyl radicals, there are endless correlations between any given set of BDE's and molecular parameters. Success in such exercises proves little. To add significantly to our understanding of these systems, an analysis must be able to explain a moderately broad set of data (i.e., both C−H and C−C BDE's) and be supported by independent data. In this case, the authors limited their analysis to the single set of BDE's that would support their case, C−H bonds. However, the direction of the deviation that is observed in Figure 2 for C−C BDE's is inconsistent with modern data on 1,3 interactions and therefore strongly suggests that the authors' interpretation is wrong. In addition, Ingold and DiLabio provided no theoretical or experimental support for the crux of their argument—the orbital overlap involved in the hyperconjugative interaction of a radical is exactly as efficient as the π-interaction in the allyl radical at providing stabilization to a system.

This lab recently presented an analysis of alkane/alkyl radical stability based on differences in 1,3 repulsive interactions.[29] The analysis accounts for trends in C−H as well as C−C BDE's and can be extended to alkenes. Although this analysis has faced criticism because the 1,3 interaction terms were derived from a fitting scheme, it must be pointed out that the model is based on a molecular interaction that has been identified, validated, and quantified by multiple research groups over 75 years. As stated clearly in the original paper, the strength of the model is not the quality of the parameter fitting, but the fact that it is built on an intramolecular interaction that has support from multiple, independent sources. This model indicates that hyperconjugation plays at most only a minor role in stabilizing alkyl radicals.[7,29]

In summary, the Ingold/DiLabio analysis of EPR data does not provide compelling evidence that hyperconjugation is the root of variations in C−H BDE's. Their model markedly fails when extended to C−CH_3 bonds and the assumption that orbital overlap plays no role in the relative efficiencies of stabilization from hyperconjugation and π-conjugation is counterintuitive and without theoretical support. Moreover, the deviation observed when their model is applied to C−CH_3 bonds suggests that hyperconjugation must play at most a minor role in stabilizing alkyl radicals. The correlation they have observed appears to be another example of a coincidental relationship resulting from the regular patterns found in BDE's and the high degree of autocorrelation found between many of the structural/electronic features of alkanes/alkyl radicals.

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(24) The evidence for repulsive 1,3 interactions is derived from a variety of experiments from different research groups that were designed to specifically probe this interaction. These experiments have consistently indicated that they are repulsive. In contrast, the effect of branching on alkane heats of formation involves a multitude of structural changes along with the development of 1,3 carbon−carbon interactions. For example, the isomerization from butane to isobutane involves a shift from a system with six 1° C−H bonds and four 2° C−H bonds to a system with nine 1° C−H bonds and one 3° C−H bond. In the absence of independent, supporting data, it is a wholly arbitrary decision to assign the energy change specifically to the development of more methyl/methyl 1,3 interactions in the branched alkanes.

(25) Wodrich, M. D.; Schleyer, P. v. R. *Org. Lett.* **2006**, *8*, 2135.

(26) Cignitti, M.; Allen, T. L. *J. Chem. Phys.* **1965**, *43*, 4472.

(27) Pitzer, K. S.; Catalano, E. *J. Am. Chem. Soc.* **1956**, *78*, 4844.

(28) Mulliken showed that a molecular orbital model of hyperconjugation could be parameterized to fit the C−H BDE's of alkanes. It should be noted that the model fit the BDE values circa 1950, which are quite different from today's values (the 3° C−H bond in isobutane was believed to 16 rather 8.5 kcal/mol weaker than the C−H bond in methane). This highlights the emprical nature of the fitting scheme: Muller, N.; Mulliken, R. S. *J. Am. Chem. Soc.* **1958**, *80*, 3489.

(29) Gronert, S. *J. Org. Chem.* **2006**, *71*, 1209.