Manifestations of Stereoelectronic Interactions in $^1J_{C-H}$ One-Bond Coupling Constants

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ABSTRACT

Two-electron/two-orbital hyperconjugative interactions depend on the relative orientation of bonds and lone pairs in a molecule and are also inversely proportional to the energy difference between the interacting orbitals. Spectroscopic manifestations of stereoelectronic interactions are particularly useful experimental signatures of these effects which can be utilized for testing molecular models. Empirical observations together with theoretical interpretations in cyclohexane and six-membered heterocycles confirm the relevance of $\sigma_{C-H_{ax}} \rightarrow \sigma^*_{C-H_{ax}}$, $n_X \rightarrow \sigma^*_{C-H_{ax}}$ (X = O or N), $\sigma_{C-S} \rightarrow \sigma^*_{C-H_{eq}}$, $\beta\text{-}n_O \rightarrow \sigma^*_{C-H_{eq}}$, $\sigma_{C(2)-H_{ax}} \rightarrow \pi^*_{C=Y}$ (Y = O, S, or CH$_2$), and $\sigma_{C(2)-H_{ax}} \rightarrow \sigma^*_{S-O_{ax}}$ two-electron/two-orbital stereoelectronic interactions that weaken the acceptor (or donor) C–H bonds and attenuate the Fermi contribution to the one-bond ^{13}C–^1H coupling constants.

Introduction

Modern organic chemistry interprets chemical reactions in terms of productive interactions between electronic orbitals that are properly oriented among themselves; in this way, the concept of stereoelectronic effects is essential for a proper understanding of molecular properties and reactivity. Interactions involving π bonds are well-recognized in many important chemical phenomena such

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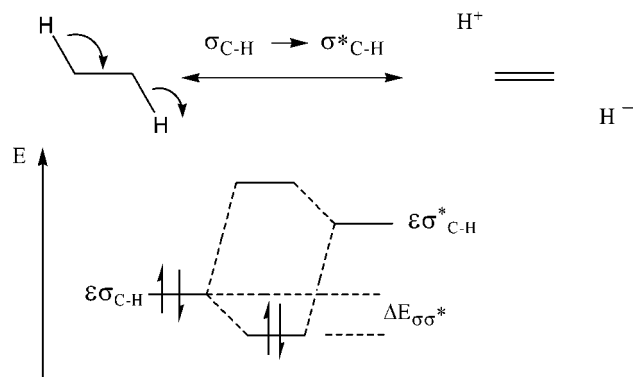
FIGURE 1. Hyperconjugative donor–acceptor interaction involving a filled σ_{C-H} orbital and an unfilled σ^*_{C-H} orbital.

as conjugation and aromaticity. By contrast, interactions involving σ bonds (hyperconjugation) have been studied less.

The concept of hyperconjugation was introduced many years ago by Mulliken[1] and has been fruitfully used to explain fundamental phenomena such as the anomeric effect[2a] and the attractive gauche effect.[2b] In particular, negative hyperconjugation refers to the lowering of the total energy in a molecule (or between molecules) as the result of interaction between filled (donor) and unfilled (acceptor) orbitals.

Nevertheless, few organic chemistry textbooks discuss hyperconjugative stereoelectronic interactions on the same level or with the same frequency as steric and electrostatic interactions when explaining chemical reactivity or the conformational behavior of organic molecules. This situation was forcefully exhibited by Weinhold[3a] and Pophristic and Goodman[3b] when they examined the origin of the rotational barrier of ethane.

In the case of ethane, the hyperconjugative interaction that stabilizes the staggered conformation over the eclipsed conformation involves partial electron transfer from an occupied σ C–H bond (σ_{C-H} orbital) to a vacant (antibonding) orbital in the antiperiplanar C–H bond (σ^*_{C-H}). This energy lowering is given by the formula

$$\Delta E_{\sigma\sigma^*} = -2 <\sigma|F|\sigma^*>/\epsilon_{\sigma^*} - \epsilon_{\sigma} \qquad (1)$$

where F is the Fock operator and ϵ_{σ} and ϵ_{σ^*} are the orbital energies.[4]

Thus, the strengths of the perturbative stabilizing interaction can be related to the shapes of the bonding and antibonding orbitals, their relative energies, and their orientation, in terms of the principle of maximum overlap between bonds and antibonds. In the case of ethane, the mixing of adjacent σ_{C-H} and σ^*_{C-H} is more favorable in the staggered conformation, so the interacting bonds adopt an antiperiplanar orientation (Figure 1).

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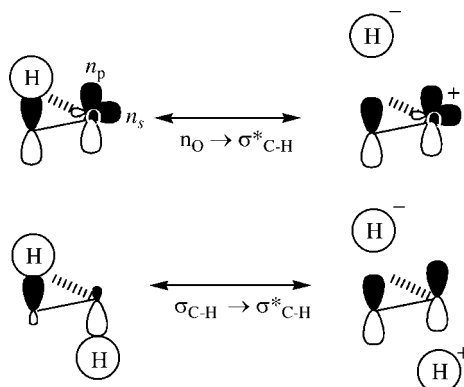
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FIGURE 2. Symmetry-adapted orbitals in $n_O \rightarrow \sigma^*_{C-H}$ and $\sigma_{C-H} \rightarrow \sigma^*_{C-H}$ negative hyperconjugation.

Since the stabilizing interaction is inversely proportional to the energy difference between the interacting orbitals, there is a stereoelectronic preference for conformations in which the best donor orbital is antiperiplanar to the best acceptor bond.[2a] In this regard, the most effective donor is a carbanion's lone pair (n_{C^-}) followed by unshared electron pairs in heteroatoms, and then σ C–H bonds. As a consequence, $n \rightarrow \sigma^*$ interactions will usually be stronger than $\sigma \rightarrow \sigma^*$ effects. Figure 2 presents symmetry-adapted orbitals in $n_O \rightarrow \sigma^*_{C-H}$ and $\sigma_{C-H} \rightarrow \sigma^*_{C-H}$ negative hyperconjugation.

One of the reasons stereoelectronic effects are not yet fully accepted as a "proved" concept is the indirect nature of the evidence that is usually advanced to support its relevance. Nevertheless, various studies during the past 15 years have provided strong evidence that empirical and theoretical analysis of one-bond C–H coupling constants is a powerful tool for the identification of stereoelectronic interactions. In particular, coupling trends can be rationalized in terms of stereospecific interactions involving $\sigma \rightarrow \sigma^*$, $\sigma \rightarrow \pi^*$, and $n \rightarrow \sigma^*$ electron delocalization. Furthermore, coupling trends usually correlate as well with structural parameters such as bond length and reactivity.

This Account summarizes salient observations in the period of 1992–2006, using various six-membered heterocyclohexanes, where the favorable antiperiplanar arrangement between the donor and acceptor orbitals is usually present. Nevertheless, the results obtained with these six-membered rings should be valid for open chain and larger molecules. This Account should also be of interest to theoretically inclined organic chemists because it describes how a theoretical concept of widespread importance can be probed with adequately designed experiments. The practical value of this research is also significant because the results can be used for structural assignments in cyclic organic molecules containing O, S, and N atoms and other heteroatoms.

Perlin Effect

In 1957, F. Bohlmann made the important observation that C–H bonds antiperiplanar (app) to a vicinal nitrogen lone pair in conformationally defined amines present characteristic infrared stretching frequencies (now known
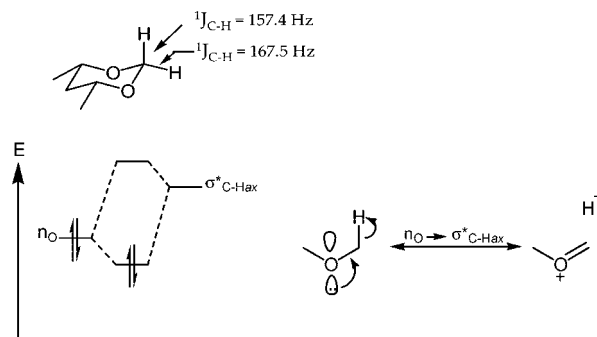

FIGURE 3. Stereoelectronic interpretation of the smaller $^1J_{C-H}$ in the axial C–H bond adjacent to oxygen.
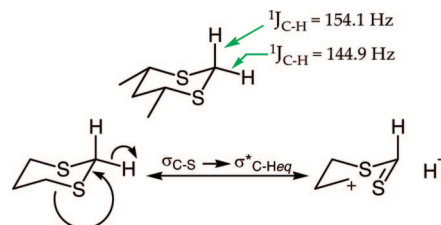

FIGURE 4. Stereoelectronic interpretation of the smaller $^1J_{C-H}$ in the equatorial C–H bond adjacent to sulfur.

as "Bohlmann bands").[5] Subsequent computational studies with methylamine indicated that the C–H$_{app}$ bond is indeed longer and weaker than the C–H$_{gauche}$ bonds,[6] and these findings have been interpreted as being the consequence of $n_N \rightarrow \sigma^*_{C-H_{app}}$ hyperconjugation (eq 2).

$$\text{(2)}$$
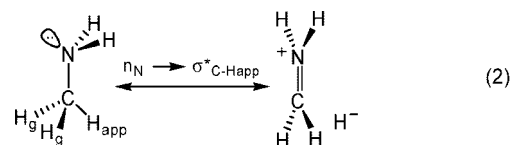
In this regard, Perlin and Casu[7] observed that the magnitude of the one-bond coupling constant for an axial C–H bond adjacent to oxygen or nitrogen in a six-membered ring is smaller by 8–10 Hz than $^1J_{C-H}$ for an equatorial C–H bond; i.e., $^1J_{C-H_{eq}} > {}^1J_{C-H_{ax}}$. This finding has been interpreted in terms of an $n_X \rightarrow \sigma^*_{C-H_{app}}$ interaction between a pair of nonbonded electrons on oxygen or nitrogen and the axial (antiperiplanar) adjacent C–H bond; that is, double bond–no bond resonance weakens the C–H$_{ax}$ bond and attenuates the one-bond $^{13}C-^1H$ coupling constant (Figure 3).

In contrast with the situation in *cis*-4,6-dimethyl-1,3-dioxane where $^1J_{C(2)-H_{ax}} < {}^1J_{C(2)-H_{eq}}$, Bailey et al.[8] reported in 1988 that the dithiane analogue exhibits an opposite behavior: $^1J_{C(2)-H_{ax}} = 154.1$ Hz $> {}^1J_{C(2)-H_{eq}} = 144.9$ Hz. This reversal of the relative magnitudes of the coupling constants at C(2) in dioxanes and dithianes was explained by Wolfe et al.[9] as a result of dominant $\sigma_{C-S} \rightarrow \sigma^*_{C-H_{eq}}$ or $\sigma_{C-H_{eq}} \rightarrow \sigma^*_{C-S}$ (rather than $n_S \rightarrow \sigma^*_{C-H_{ax}}$) interactions in the dithiane (Figure 4).

Chart 1

^1J values in Hz. At -90°C, in methylene chloride-d_2.
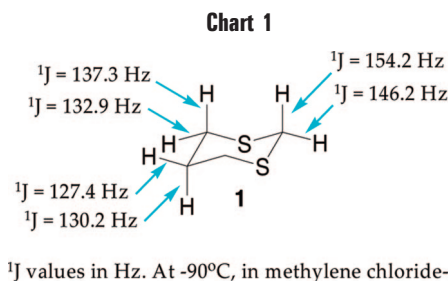
Experimental Determination of $^1J_{C-H}$ Coupling Constants of All Bonds in 1,3-Dithiane[10]

All equatorial C–H bonds in 1,3-dithiane (**1**) are antiperiplanar (app) to C–S bonds in the ring. Thus, should $\sigma_{C-S} \rightarrow \sigma^*_{C-H_{eq}}$ or $\sigma_{C-H_{eq}} \rightarrow \sigma^*_{C-S}$ stereoelectronic interactions dominate over $n_S \rightarrow \sigma^*_{C-H_{ax}}$ interactions, one would expect $^1J_{C-H_{ax}}$ to be greater than $^1J_{C-H_{eq}}$ for all C-H one-bond couplings in 1,3-dithiane. Indeed, the values of the $^1J_{C-H}$ coupling constants, determined from the proton-coupled ^{13}C NMR spectra, show this to be the case; all axial H(2) protons in **1** present the larger $^1J_{C-H}$ coupling constant (Chart 1). This finding is in line with a dominant $\sigma_{C-S} \rightarrow \sigma^*_{C-H_{eq}}$ and/or $\sigma_{C-H_{eq}} \rightarrow \sigma^*_{C-S}$ hyperconjugative interactions that weaken the equatorial C–H bond.

In 1,3-dithiane **1**, the donor capacity of the σ C–S orbital toward the σ^* C–H$_{eq}$ antibonding orbital evidently surpasses that of the "anomeric type" $n_S \rightarrow \sigma^*_{C-H_{ax}}$ interaction that weakens the axial C(2)–H$_{ax}$ bond. Furthermore, the equatorial C(2)–H bond in 1,3-dithiane **1** is also weakened by a simultaneous $\sigma(C-H_{eq})$ to $\sigma^*(S-C)$ two-orbital/two-electron interaction. Indeed, it has been shown that the $\sigma^*(S-C)$ orbital is a better acceptor than the $\sigma^*(O-C)$ orbital.[11,12] The poor donor ability of the sulfur lone pair toward the adjacent σ^* C–H$_{ax}$ orbital is a consequence of the diffuse nature of the former orbital, in contrast with the hard character of the latter.

Experimental Determination of All $^1J_{C-H}$ Bonds in 1,3-Dioxane and Its Derivatives[10]

In agreement with previous reports,[7b] the ^1J for the C(2)–H$_{ax}$ bond in 1,3-dioxane **2** is smaller by 8.9 Hz than the ^1J for the C(2)–H$_{eq}$ bond (Figure 3). As already mentioned in the Introduction, this phenomenon can be rationalized in terms of a dominant $n_O \rightarrow \sigma^*_{C-H_{ax}}$ interaction between a p-type[13] lone electron pair orbital on oxygen and the axial (app) C–H bond on the adjacent C(2).

By contrast, $^1J_{C-H_{eq}} = {}^1J_{C-H_{ax}} = 128.9$ Hz for the meth-

ylenic C–H bonds at C(5) (Figure 5a). To explain the apparent weakening of the equatorial C(5)–H bond, which counterbalances the hyperconjugative $\sigma_{C-H} \rightarrow \sigma^*_{C-H}$ interactions between the antiperiplanar C(5)–H and C(4,6)–H bonds,[14] Anderson et al.[15] suggested a stereoelectronic interaction between a pseudoequatorial nonbonding electron pair on a β-oxygen and the equatorial C–H bond through a W arrangement of orbitals. Nevertheless, Alabugin[16] subsequently showed that the pseudoaxial p-type pair is a better electron donor and is suitably disposed for through-space interaction with the back lobe of the antibonding C(5)–H$_{eq}$ orbital (Figure 5b).

Theoretical Study of Stereoelectronic Effects on the Magnitude of One-Bond $^1J_{C-H}$ Coupling Constants[17]

In recent years, molecular modeling methods based on the postulates and theorems of quantum mechanics have proven to be an extremely powerful technique for the reliable calculation of physical observables.[18] One-bond C–H coupling constants, $^1J_{C-H}$, are amenable to accurate computation, and in particular, ab initio calculations that take into account electron correlation are convenient in the study of stereoelectronic effects. In most of the work summarized in this Account, calculations were carried out using density functional theory [DFT, B3LYP/6-31G(d,p)].[19] The 6-31G** basis set is commonly used in computational studies of the anomeric effect, and the diffuse orbital-augmented basis set [6-31+G(d,p)] was used to take into account the relatively diffuse nature of the lone pairs.[20]

Cyclohexane (**3**) and oxygen-, sulfur-, and/or nitrogen-containing six-membered heterocycles **4–7** (Chart 2) were studied theoretically. Density functional theory [B3LYP/6-31G(d,p)] was able to reproduce the structure (in particular C–H bond distances). The density functional calculation of $^{13}C-{}^1H$ coupling constants was conducted using the approach proposed by Malkin, Malkina, and Salahub.[21] Within this methodology, three contributions to the NMR spin–spin coupling constants are considered, namely, the Fermi contact, the paramagnetic spin orbit, and the diamagnetic spin orbit. These spin–spin coupling constant calculations were conducted with a modified version of deMon-KS.[22] The results confirmed the importance of $n_X \rightarrow \sigma^*_{C-H_{app}}$ (where X = O or N), $\sigma_{S-C} \rightarrow \sigma^*_{C-H_{app}}$, $\sigma_{C-S} \rightarrow \sigma^*_{C-H_{app}}$, β-$n_O \rightarrow \sigma^*_{C-H}$, and $\sigma_{C-H} \rightarrow \sigma^*_{C-H_{app}}$ hyperconjugation.
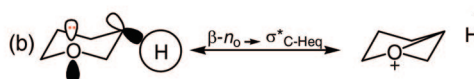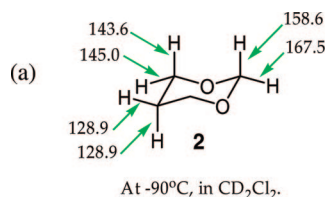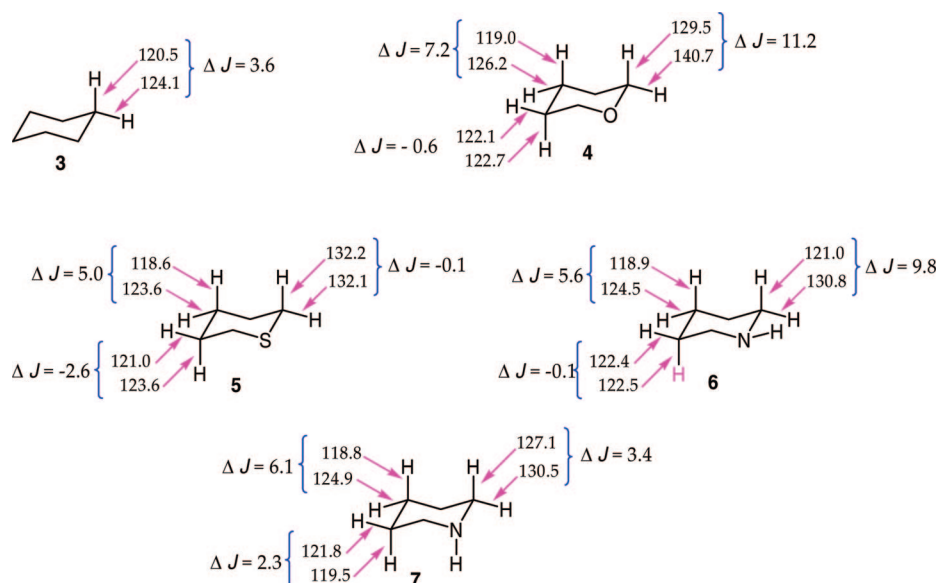

At -90°C, in CD$_2$Cl$_2$.

FIGURE 5. (a) Experimentally obtained one-bond coupling constants in 1,3-dioxane **2** (from ref 10). (b) Through-space hyperconjugative interaction between a p-type lone pair at the β-oxygen and the back lobe of the antibonding C(5)-H$_{eq}$ orbital. Reprinted with permission from ref 16. Copyright 2003 American Chemical Society.

Chart 2

Cyclohexane **3** served as the parent, reference compound, whereas heterocycles **4**–**7** provided the fundamental information about the consequences of replacement of a methylene group in cyclohexane with oxygen (**3** → **4**), sulfur (**3** → **5**), an equatorial NH group (**3** → **6**), and an axial NH group (**5** → **7**). Specifically, all C–H bond lengths in **4**–**7** are compared with the reference C–H$_{ax}$ and C–H$_{eq}$ bond lengths in cyclohexane: any C–H bond lengthening observed in **4**–**7** might reflect stereoelectronic interactions, where σ^*_{C-H} is the acceptor orbital. (Nevertheless, interactions where σ_{C-H} is a donor orbital, as in $\sigma_{C-H_{ax}} \rightarrow \sigma^*_{C-H_{ax}}$ hyperconjugation, should also result in C–H bond lengthening since electron density is removed from a bonding orbital.) Furthermore, although longer C–H bonds are *not* always associated with smaller one-bond C–H coupling constants,[16a,23] weaker C–H bonds are expected to be associated with smaller $^1J_{C-H}$ coupling constants.[7,9,10]

Chart 2 presents the calculated one-bond $^{13}C-^1H$ coupling constants (hertz) for cyclohexane (**3**) and monoheterocyclohexanes **4**–**7**. To facilitate the analysis of the collected data, Chart 2 also includes the difference $\Delta J_{ax/eq} = J_{C-H_{eq}} - J_{C-H_{ax}}$ for each distinct methylene in the molecule. Positive ΔJ values reflect then normal "Perlin effects",[9a] that is, typical situations where $\sigma_{C-H_{ax}} \rightarrow \sigma^*_{C-H_{app}}$ and/or $n_X \rightarrow \sigma^*_{C-H_{app}}$ stereoelectronic interactions lead to weaker axial C–H bonds and smaller $^1J_{C-H_{ax}}$ coupling constants, relative to $^1J_{C-H_{eq}}$.

With respect to the reference cyclohexane (**3**) molecule, calculations reproduce the relative magnitude of both the C–H$_{ax}$ and C–H$_{eq}$ coupling constants, that is, the normal Perlin effect observed in cyclohexane, as well as the absolute values, within reasonable limits (±2–3 Hz). Indeed, the calculated values ($^1J_{C-H_{ax}}$ = 120.5 Hz and $^1J_{C-H_{eq}}$ = 124.1 Hz) are to be compared with the corresponding experimental values, 122.4 and 126.4 Hz, respectively.[24]

Three distinct methylenic pairs of C–H bonds exist in oxane **4**. As anticipated, $n_O \rightarrow \sigma^*_{C-H_{app}}$ hyperconjugation weakens the axial C–H bonds at C(2) and C(6) so that the

$^1J_{C(2,6)-H_{ax}}$ of 129.5 Hz is significantly smaller than the $^1J_{C(2,6)-H_{eq}}$ of 140.7 Hz; thus, the calculated $\Delta^1J_{ax/eq}$ is 11.2 Hz. In strong contrast, $^1J_{C(3,5)-H_{ax}}$ = 122.7 Hz > $^1J_{C(3,5)-H_{eq}}$ = 122.1 Hz, and $\Delta^1J_{ax/eq}$ = −0.6 Hz. This *reverse* correlation of ^1J values relative to cyclohexane is in agreement with the β-$n_O \rightarrow \sigma^*_{C(5)-H_{eq}}$ stereoelectronic interaction advanced by Alabugin[16] (Figure 5b). Finally, the calculated coupling constants for the methylenic C–H bonds at C(4) [$^1J_{C(4)-H_{ax}}$ = 119.0 Hz < $^1J_{C(4)-H_{eq}}$ = 126.2 Hz; $\Delta^1J_{ax/eq}$ = 7.2 Hz] are those expected for a "cyclohexane-like" methylenic segment.

The one-bond C–H coupling constants calculated for thiane **5** reveal two effects. (1) At C(2), where $n_S \rightarrow \sigma^*_{C(2)-H_{ax}}$ hyperconjugation is not relevant, $\sigma_{C(3)-H} \rightarrow \sigma^*_{C(2)-H_{ax}}$ interaction is offset by a dominant $\sigma_{C(6)-S} \rightarrow \sigma^*_{C(2)-H_{eq}}$ stereoelectronic effect, and (2) at C(3), $^1J_{C-H_{eq}} < ^1J_{C-H_{ax}}$ (121.0 and 123.6 Hz, respectively). This observation is best interpreted in terms $\sigma_{S-C(2)} \rightarrow \sigma^*_{C(3)-H_{eq}}$ electron transfer that is apparently more important than two $\sigma_{C-H} \rightarrow \sigma^*_{C(3)-H_{ax}}$ and two $\sigma_{C(3)-H_{ax}} \rightarrow \sigma^*_{C-H}$ hyperconjugative interactions. Other interactions that weaken the equatorial C(3)–H bond are $\sigma_{C(3)-H_{eq}} \rightarrow \sigma^*_{S-C(2)}$, $\sigma_{C(3)-H_{eq}} \rightarrow \sigma^*_{C(4)-C(5)}$, and $\sigma_{C(4)-C(5)} \rightarrow \sigma^*_{C(3)-H_{eq}}$ interactions, although these contributions are anticipated to be less important in view of the weaker acceptor ability of the σ^*_{S-C} and σ^*_{C-C} orbitals, as well as the poor donor ability of the σ_{C-C} orbital.[12,17]

Analysis of the $^1J_{C-H}$ coupling constants in azanes **6** and **7** is particularly interesting because of the possible consequences of the pseudoaxial and pseudoequatorial orientation of the nitrogen lone pair in these models. Indeed, in azane **6** (equatorial N–H bond), a substantial Perlin effect is appreciated at C(2): $^1J_{C-H_{ax}}$ = 121.0 Hz < $^1J_{C-H_{eq}}$ = 130.8 Hz; $\Delta^1J_{ax/eq}$ = 9.8 Hz. By contrast, in azane **7**, where the nitrogen lone pair is gauche to both C(2)–H bonds, a much diminished normal Perlin effect is found: $\Delta^1J_{ax/eq}$ = 3.4 Hz. Importantly, in azane **6**, $^1J_{C(3)-H_{ax}} \approx ^1J_{C(3)-H_{eq}}$ = 122.5 Hz, whereas in epimeric azane **7**, the normal trend is observed [$^1J_{C(3)-H_{ax}}$ = 119.5 Hz < $^1J_{C(3)-H_{eq}}$ = 121.8 Hz]. This result does fit expectation in terms of β-$n_{N_{ax}} \rightarrow \sigma^*_{C(3)-H_{eq}}$ hyperconjuga-

Chart 3
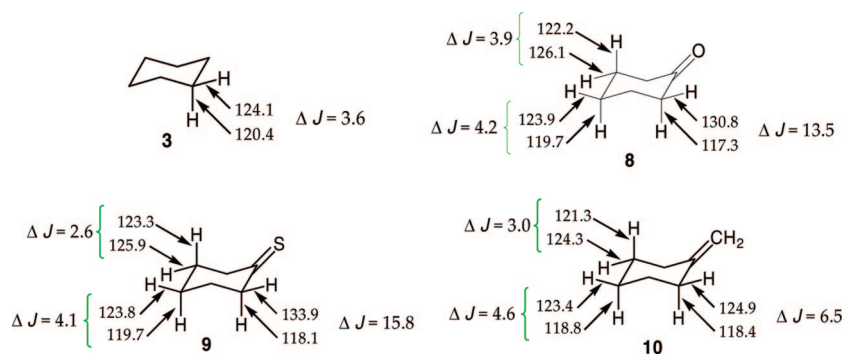
tion (cf. Figure 5b). Finally, normal Perlin effects ($^1J_{C–H_{ax}}$ < $^1J_{C–H_{eq}}$) are seen at C(4), in both **6** and **7**.

Relative Acceptor Ability of the Carbonyl (C=O), Thiocarbonyl (C=S), and Methylidene (C=CH₂) Groups toward C–H Donor Bonds[25]

A different form of hyperconjugation has been documented for substituted π systems. In particular, σ C–H bonds can in principle act as donors of electrons to adjacent π double bonds or carbonyl groups as depicted in eq 3.[26]
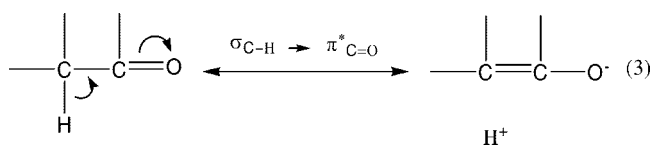
A computational study aimed at determining the relative importance of hyperconjugative interactions involving σ C–H donor bonds and the carbonyl π system as the acceptor orbital sought manifestation of $\sigma_{C–H} \rightarrow \pi^*_{C=O}$ stereoelectronic interaction upon the magnitude of calculated $^1J_{C–H}$ coupling constants. Cyclohexanone **8** (eq 4) allows determination of any effect that the presence of the carbonyl group has on the strength of the C–H bond for the ring methylenes. In particular, axial C–H$_{ax}$ bonds adjacent to the carbonyl π system should participate in $\sigma_{C–H_{ax}} \rightarrow \pi^*_{C=O}$ hyperconjugation, leading to weaker bonds. By contrast, equatorial C–H$_{eq}$ bonds adjacent to the carbonyl are essentially orthogonal to the π orbital so that $\sigma_{C–H_{eq}} \rightarrow \pi^*_{C=O}$ hyperconjugation will be negligible. Thus, it is anticipated that for the methylenic groups adjacent to the carbonyl, $^1J_{C–H_{ax}} < {}^1J_{C–H_{eq}}$.
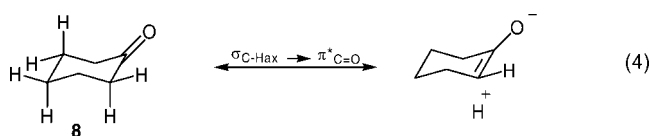

Figure 6 collects the structural data for cyclohexane **3**, cyclohexanone **8**, thiocyclohexanone **9**, and methylenecyclohexene **10**. As discussed above, the slightly longer (and thus weaker) axial C–H bond in cyclohexane (C–H$_{ax}$ = 1.100 Å vs C–H$_{eq}$ = 1.098 Å) is the result of $\sigma_{C–H_{ax}} \rightarrow \sigma^*_{C–H_{ax}}$ hyperconjugation between antiperiplanar bonds.

Although the difference in bond length between axial and equatorial C–H bonds in cyclohexane is small ($r_{C–H_{ax}} - r_{C–H_{eq}} = 0.002$ Å), it becomes quite large for methylenes adjacent to the carbonyl group in cyclohexanone **8** [$r_{C(2)–H_{ax}} - r_{C(2)–H_{eq}} = 1.100 - 1.093 = 0.007$ Å]. Surprisingly, the difference in bond length in methylenic C–H bonds that are adjacent to the thiocarbonyl group in thiocyclohexanone **9** is calculated to be even larger [$r_{C(2)–H_{ax}} - r_{C(2)–H_{eq}} = 1.101 - 1.092 = 0.009$ Å]. By contrast, $\Delta r_{C–H_{ax,eq}}$ for the methylenes adjacent to the C=CH₂ methylidene group in **10** is smaller than that observed in cyclohexanone **8** (0.006 and 0.007 Å, respectively).

The structural data presented in Figure 6, in particular, the differences in bond lengths between axial and equatorial C(2)–H bonds suggest that $\sigma_{C–H_{ax}} \rightarrow \pi^*_{C=Y}$ and/or $\pi_{C=Y} \rightarrow \sigma^*_{C–H_{ax}}$ hyperconjugation (Scheme 1) is most effective with the thiocarbonyl group, followed by the carbonyl and, finally, the methylidene group.

Chart 3 includes the difference $\Delta J_{ax/eq} = J_{C–H_{eq}} - J_{C–H_{ax}}$ for each distinct methylene in the molecule. The positive ΔJ values reflect $\sigma_{C–H_{ax}} \rightarrow \sigma^*_{C–H_{ax}}$, $\sigma_{C–H_{ax}} \rightarrow \pi^*_{C=Y}$, and/or $\pi_{C=Y} \rightarrow \sigma^*_{C–H_{ax}}$ stereoelectronic interactions leading to weaker axial C–H bonds with smaller $^1J_{C–H_{ax}}$ coupling constants relative to $^1J_{C–H_{eq}}$. Most relevant is the fact that the calculated difference ($\Delta J_{ax/eq}$) for the methylenic C(2,6)–H bonds adjacent to the exocyclic C=Y bonds decreases in the following order: thioketone **9** ($\Delta J_{ax/eq}$ = 15.8 Hz) > ketone **8** ($\Delta J_{ax/eq}$ = 13.5 Hz) > methylenecyclohexane **10** ($\Delta J_{ax/eq}$ = 6.5 Hz, which is, nevertheless, larger than the $\Delta J_{ax/eq}$ of 3.6 Hz that is found in reference compound cyclohexane **3**). This trend is, of course, in line with the structural evidence reported in Figure 6 and indicates that the relative acceptor ability of the π bonds
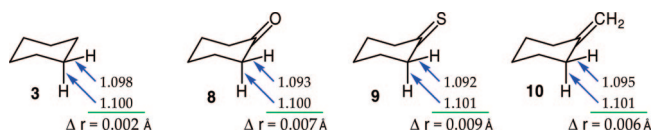

FIGURE 6. Difference in axial vs equatorial C–H bonds in cyclohexane **3**, cyclohexanone **8**, thiocyclohexanone **9**, and methylenecyclohexane **10**.
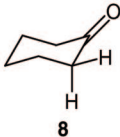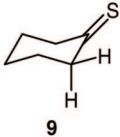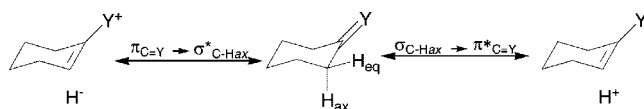
Scheme 1

Table 1. Selected Hyperconjugative Interactions (E_{del}) for C(2,6)–H Bonds Adjacent to the C=Y Acceptor Group in Cyclohexanone 8 (Y = O), Thiocyclohexanone 9 (Y = S), and Methylenecyclohexane 10 (Y = CH$_2$)
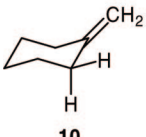
donor orbital	acceptor orbital	E_{del} (kcal/mol)	ΔE donor/acceptor (Hartrees)
$\sigma_{C(2,6)-Hax}$	σ^*_{C-O}	1.20	1.11
$\sigma_{C(2,6)-Hax}$	$\pi^*_{C=O}$	**5.47**	**0.53**
$\sigma_{C(2,6)-Heq}$	σ^*_{C-O}	1.24	1.11
$\sigma_{C(2,6)-Heq}$	$\pi^*_{C=O}$	0.05	0.53
σ_{C-O}	$\sigma^*_{C(2,6)-Hax}$	-0.32	1.51
$\pi_{C=O}$	$\sigma^*_{C(2,6)-Hax}$	2.46	0.80
$\sigma_{C(2,6)-Hax}$	σ^*_{C-S}	2.28	0.82
$\sigma_{C(2,6)-Hax}$	$\pi^*_{C=S}$	**7.32**	**0.45**
$\sigma_{C(2,6)-Heq}$	σ^*_{C-S}	0.05	--
$\sigma_{C(2,6)-Heq}$	$\pi^*_{C=S}$	0.00	--
σ_{C-S}	$\sigma^*_{C(2,6)-Hax}$	0.76	1.17
$\pi_{C=S}$	$S^*_{C(2,6)-Hax}$	3.53	0.7
$\sigma_{C(2,6)-Hax}$	S^*_{C-C}	1.62	1.16
$\sigma_{C(2,6)-Hax}$	$\pi^*_{C=C}$	**5.79**	**0.55**
$\sigma_{C(2,6)-Heq}$	σ^*_{C-C}	0.12	--
$\sigma_{C(2,6)-Heq}$	$\pi^*_{C=C}$	0.02	--
σ_{C-CH2}	$\sigma^*_{C(2,6)-Hax}$	0.44	1.17
$\sigma_{C=CH2}$	$\sigma^*_{C(2,6)-Hax}$	4.86	0.70

diminishes in the following order: C=S > C=O > C=CH$_2$. Apparently, the C=S group is a stronger acceptor even though O is more electronegative than S due to the energy gap decrease for C–S antibond orbitals (see below). Thus, the better the π acceptor, the greater the contribution of the double bond–no bond delocalized form to the molecule and the weaker the σ C–H bond (cf. eq 3).

Simultaneously, the potential role of $\pi_{C=Y} \rightarrow \sigma^*_{C-H_{ax}}$ hyperconjugation must be considered. In this regard, natural bond orbital (NBO) analysis is a state-of-the-art theoretical technique developed by Weinhold[27] that allows one to estimate the energy of hyperconjugative effects quantitatively and to unravel their relative importance. The NBO analysis transforms the canonical delocalized Hartree–Fock (HF) MOs into localized hybrid orbitals (NBOs). Filled NBOs describe the hypothetical, strictly localized Lewis structures. The interactions between filled and empty antibonding orbitals represent the deviation of the molecule from the Lewis structure and can be used as a measure of delocalizations. In particular, NBO analysis gives the energies of the delocalizing interactions that are weakening the C–H bonds of interest. These energies (E_{del}) are obtained by the deletion of the corre-

sponding Fock elements and followed by the recalculation of the wave function.

Table 1 summarizes the NBO-estimated energies of deletion (E_{del}) for the main hyperconjugative interactions in cyclohexanone **8**, thiocyclohexanone **9**, and methylenecyclohexane **10**. Table 1 includes the calculated difference in energy between the donor and acceptor orbitals of interest. As expected, the magnitude of the two-electron/two-orbital hyperconjugative interaction depends inversely on the energy gap between the donor and acceptor orbitals. Thus, as evidenced by the analysis of the C–H bond strength presented above, the smaller energy difference encountered in thioketone **9** ($\Delta E = 0.45$ hartree) results in a stronger delocalizing $\sigma_{C(2,6)-H_{ax}} \rightarrow \pi^*_{C=S}$ interaction ($E_{del} = 7.32$ kcal/mol) relative to the corresponding stereoelectronic interaction in cyclohexanone **10** [$E_{del} = 5.47$ kcal/mol for $\sigma_{C(2,6)-H_{ax}} \rightarrow \pi^*_{C=O}$; $\Delta E = 0.45$ hartree].

α-Heterocyclohexanones 11-14[25]

The title compounds were studied with the goal of examining the effect that electron donation from the α-heteroatom to the π system would have on the $\sigma_{C-H_{ax}}$

Chart 4

11

12

13

14
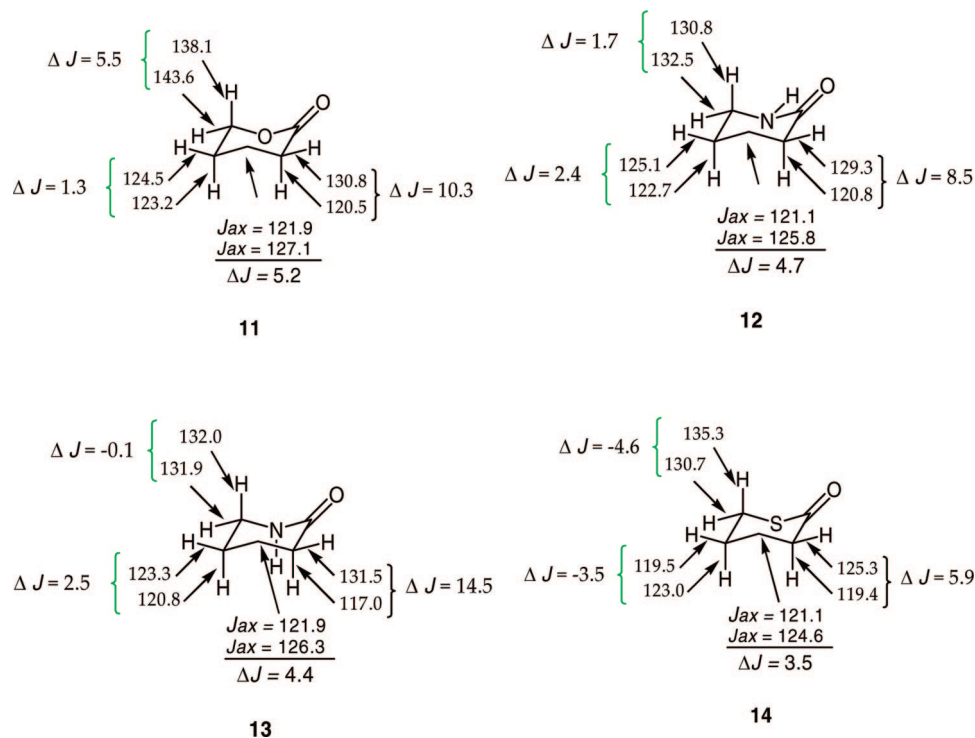
$\rightarrow \pi^*_{C=Y}$ stereoelectronic interaction that is operative in compounds **8–10**. Specifically, it is anticipated that classical conjugation in the X–C=Y segment will increase the energy of the LUMO π^* orbital, making it a less-efficient acceptor (eq 5).

(5)
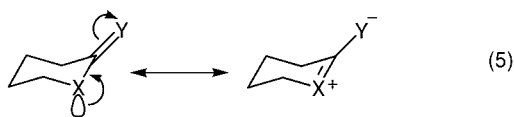
Efficient conjugation, as depicted in eq 5, should then attenuate the $\sigma_{C-H_{ax}} \rightarrow \pi^*_{C=Y}$ hyperconjugative interaction already verified in **8–10** and should be manifested in the corresponding one-bond coupling constants in six-membered lactones, lactams, and methylidene analogues **11–14**. Chart 4 collects the calculated structural and spectroscopic ($^1J_{C-H}$) data of interest.

As anticipated, conjugation between the heteroatom (X = O, N–H$_{eq}$, or S) and the π bond (C=Y, Y = O, S, or CH$_2$) places increased electron density in the π orbital and attenuates its acceptor orbital character. This effect is manifested as a diminished participation of the vicinal C(3)–H$_{ax}$ donor C–H orbital in $\sigma_{C-H} \rightarrow \pi^*$ hyperconjugation [i.e., stronger C(3)–H$_{ax}$ bonds, larger $^1J_{C(3)-H_{ax}}$ coupling constants, and smaller $\Delta^1J_{ax/eq}$ values at C(3)].

Indeed, Chart 4 shows $\Delta^1J_{ax/eq}$ values for the methylenic C–H bonds at C(3) in compounds **11**, **12**, and **14** (10.3, 8.5, and 5.9 Hz, respectively), which are significantly smaller than the corresponding $\Delta^1J_{ax/eq}$ value in the reference cyclohexanone **8** [13.5 Hz (Chart 3). By contrast, lactam **13** shows a $\Delta^1J_{ax/eq}$ of 14.5 Hz for C(3), and this value is essentially similar to that encountered in **8**. It is then appreciated that in the absence of N–C=O conjuga-

tion (in **13**) the carbonyl orbital that is more effective as an acceptor orbital to the C(3)–H$_{ax}$ donor orbital.

Thiane Sulfone[28]

Theoretical calculation of the optimized structure [B3LYP/ 6-311++G(2d,2p)] of thiane sulfone, **15**, was followed by estimation of the $^1J_{C-H}$ one-bond coupling constants [BP/ IGLO-III//B3LYP/6-311++G(2d,2p)]. Figure 7 collects the calculated data for all C–H one-bond coupling constants in **15**, which includes for the purposes of comparison the values obtained experimentally for thiane, **5**.[17] It can be anticipated
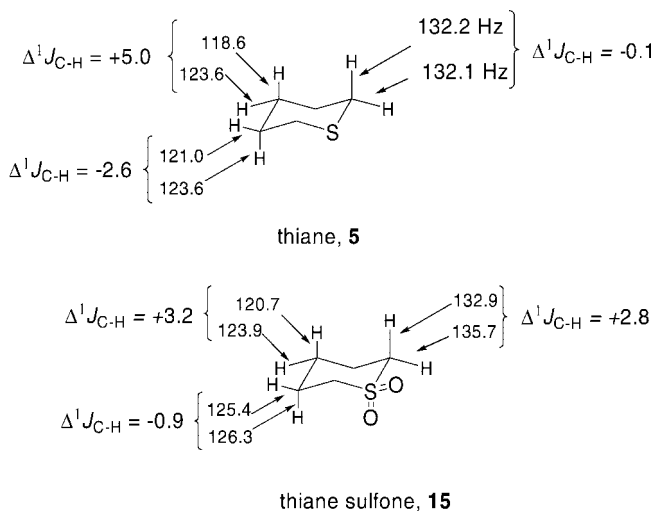

FIGURE 7. Calculated [BP/IGLO-III//B3LYP/6-311G++(2d,2p)] coupling constants in thiane **5** (from ref 17) and thiane sulfone **15** (from ref 28). Reprinted with permission from ref 17and ref 28. Copyright 2002 and 2006 American Chemical Society.
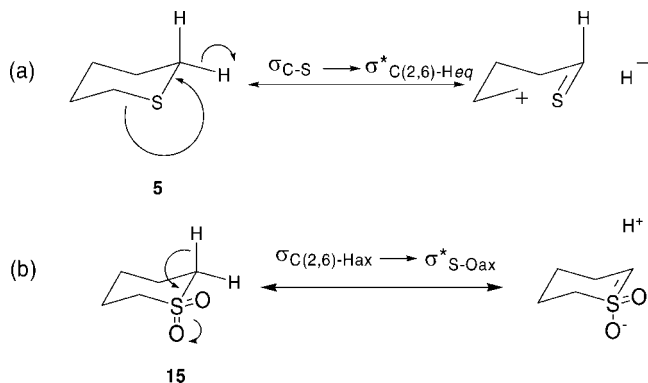
(a)

(b)

5

15

FIGURE 8. Dominant stereoelectronic interactions operative in thiane **5** [$\Delta^1 J_{C(2,6)-H} = -0.1$ Hz] and thiane sulfone **15** [$\Delta^1 J_{C(2,6)-H} = 2.8$ Hz].

that the σ_{C-SO_2} orbital in sulfone **15** will not be as effective as a donor as the donor σ_{C-S} orbital in thiane **5**.

Salient observations from the comparison of the calculated $^1J_{C-H}$ one-bond coupling constants presented in Figure 7 are as follows.

(1) The reverse Perlin effect operative at C(2,6) in thiane **5** ($\Delta^1 J_{C-H} = -0.1$ Hz) is in contrast with the normal Perlin effect observed for the same methylenic C–H bonds α to the sulfonyl group in thiane sulfone **15** ($\Delta^1 J_{C-H} = 2.8$ Hz). It is apparent then that the dominant $\sigma_{C-S} \rightarrow \sigma^*_{C(2,6)-H_{eq}}$ stereoelectronic interaction that weakens the equatorial C–H bonds adjacent to sulfur in thiane **5** (Figure 8a) is overcome by $\sigma_{C(2,6)-H_{ax}} \rightarrow \sigma^*_{S-O_{ax}}$ delocalization[29] in thiane sulfone **15**, weakening the axial C(2,6)–H$_{ax}$ bonds and resulting in the observed normal Perlin effect (Figure 8b).

(2) The substantial reverse Perlin effect [$\Delta^1 J_{C(3,5)-H} = -2.6$ Hz] found at the β-methylenes in thiane **5** dwindles significantly in thiane sulfone **15** [$\Delta^1 J_{C(3,5)-H} = -0.9$ Hz], because of the diminished donor ability of the σ_{C-SO_2} orbitals relative to σ_{C-S} donor orbitals. Thus, the C(3,5)–H$_{eq}$ bond exhibits a larger $^1J_{C-H}$ one-bond coupling constant in the sulfone, from 121.90 Hz in **5** to 125.4 Hz in **15**.

(3) No significant change in the values of the C–H one-bond coupling constants is appreciated at the more distant (relative to the sulfur group) γ-methylene.

Additional Recent Advances

(a) Dipole-Induced Dipole Electrostatic Contribution to $^1J_{C-H}$[30]. The calculation of C–H one-bond coupling constants upon rotation of the n_O–C–O–H dihedral angle τ was recently carried out at the BP/IGLO-III//B3LYP/6-311++G(2d,2p) level. It had been anticipated that $^1J_{C-H}$ would be minimal at $\tau = 90°$. Instead, it was found that $^1J_{C-H}$ decreases continually from its maximum near 180° and approaches a minimum near 0°. Although $^1J_{C-H}$ is lower at 90° than at 180°, consistent with delocalization of an antiperiplanar lone pair of electrons, the behavior depicted follows $\cos \tau$ rather than $\cos 2\tau$, and this finding was explained in terms of a contributing dipolar interaction, where the dipole moment of the lone pair induces a dipole at the C–H bond (Figure 9); i.e., the interactions at $\tau = 0°$ and 180° are opposite. This then accounts for why J values at 0° and 180° are so different and why J takes

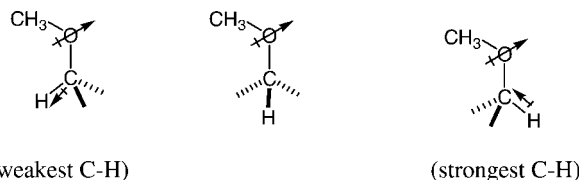(weakest C-H) (strongest C-H)

FIGURE 9. Dipole-induced dipole interactions upon variation of the dihedral angle in the H–C–O–C segment.

intermediate values between 60° and 120°, where delocalization would be maximal.

In this context, Tormena and co-workers[31] examined the participation of hyperconjugative and electrostatic interactions in $^1J_{C-H}$ coupling constants in several 1-X-bicyclo[1.1.1]pentane derivatives. Hyperconjugative interactions were calculated using the NBO approach, while electrostatic interactions were modeled with a point charge placed in the vicinity of the corresponding C–H bond. It was verified that (1) hyperconjugative interactions from σ_{C-H} bonds into the σ^*_{C-H} antibond yield a decrease in the corresponding $^1J_{C-H}$ coupling constants, and (2) such hyperconjugative interactions can be inhibited (enhanced) by electrostatic interactions depending on the orientation of the electric field.

(b) Application of $^1J_{C-H}$ Coupling Constants in Conformational Analysis. Kleinpeter et al.[32] examined recently the applicability of NMR C–H one-bond coupling constants as a tool in conformational analysis of six-membered heterocycles. In particular, (1) the conformational equilibria calculated at the HF and DFT levels of theory for a number of methyl-substituted 1,3-dioxanes, 1,3-oxathianes, and 1,3-dithianes agreed with the experimentally verified data, and (2) analysis of the average $^1J_{C-H}$ coupling constants determined from proton-coupled ^{13}C NMR spectra of those heterocyclic derivatives can be used to as a reliable indication of the conformational preference of each particular heterocycle.

(c) $^1J_{C-H}$ Correlation with the Hydrogen Bond Strength of Alcohols. Anderson and co-workers[33] have recently noticed that the strength of H-bond donation by alcohols is reflected in the one-bond C–H spin coupling constant of the H–C–O–H molecular segment. Specifically, the magnitude of $^1J_{C-H}$ decreases as the H-bond enthalpy increases. This behavior was attributed to a strengthened stereoelectronic interaction between the donor σ_{C-H} orbital and the vicinal σ^*_{O-H} acceptor orbital.

(d) Configurational Assignment of Azomethines. Krivdin and collaborators[34] have recently reported the stereochemical dependence of one-bond C–H coupling constants upon the orientation of the nitrogen lone electron pair in several isomers of azomethines. This conformational effect was interpreted in terms of a $\sigma_{C-H} \rightarrow \sigma^*_{C-X}$ (X = O, Cl, or Br) stereoelectronic interaction that weakens the C–H bond and gives rise to smaller $^1J_{C-H}$ values.

Concluding Remarks

Despite the fact that far-reaching phenomena such as the anomeric effect and the attractive gauche effects are usually interpreted in terms of stereoelectronic interac-

tions, it is fair to say that hyperconjugation is still a concept that is not given its proper due in organic chemistry. Spectroscopic manifestations of stereoelectronic interactions are particularly useful experimental signatures of these effects which can be utilized for testing models for molecular structure, reactivity, and properties. Extension of the analysis performed described here in six-membered rings to more complex systems and to compounds containing heavier heteroatoms and metals will provide a wealth of useful new data. It can be anticipated that introductory textbooks of chemistry will soon contain complete sections dedicated to the discussion of the concept of hyperconjugative interactions and the consequences with respect to conformational analysis, reaction mechanism, and spectroscopic manifestations in all branches of chemistry.

Note added in proof. Very recently, Podlech and coworkers[35] confirmed the importance of stereoelectronic effects on the magnitude of C–H one-bond coupling constants in sulfoxides and sulfones. In particular, σ_{C-Hax} → $\sigma^*_{S=Oax}$ hyperconjugation leads to a weakening of the axial C–H bonds and to a correspondingly smaller coupling.

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