JOC Article

Manifestation of Stereoelectronic Effects on the Calculated Carbon−Hydrogen Bond Lengths and One-Bond $^1J_{C-H}$ NMR Coupling Constants. Relative Acceptor Ability of the Carbonyl (C=O), Thiocarbonyl (C=S), and Methylidene (C=CH_2) Groups toward C−H Donor Bonds

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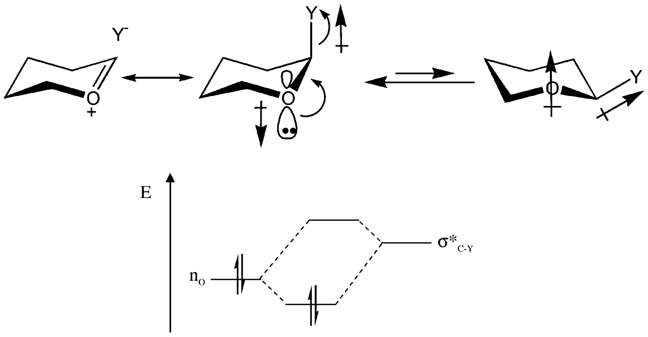
Theoretical examination [B3LYP/6-31G(*d*,*p*), PP/IGLO-III//B3LYP/6-31G(*d*,*p*), and NBO methods] of six-membered cyclohexane **1** and carbonyl-, thiocarbonyl-, or methylidene-containing derivatives **2**−**27** afforded precise structural (in particular, C−H bond distances) and spectroscopic (specifically, one-bond $^1J_{C-H}$ NMR coupling constants) data that show the consequences of stereoelectronic hyperconjugative effects in these systems. Major observations include the following. (1) $\sigma_{C-Hax} \rightarrow \pi^*_{C=Y}$ and $\pi_{C=Y} \rightarrow \sigma^*_{C-Hax}$ (Y = O, S, or CH_2) hyperconjugation leads to a shortening (strengthening) of the equatorial C−H bonds adjacent to the π group. This effect is reflected in smaller $^1J_{C-Hax}$ coupling constants relative to $^1J_{C-Heq}$. (2) Comparison of the structural and spectroscopic consequences of $\sigma_{C-Hax} \rightarrow \pi^*_{C=Y}$ hyperconjugation in cyclohexanone **2**, thiocyclohexanone **3**, and methylenecyclohexane **4** suggests a relative order of acceptor orbital ability C=S > C=O > C=CH_2, which is in line with available pK_a data. (3) Analysis of the structural and spectroscopic data gathered for heterocyclic derivatives **5**−**12** reveals some additivity of $\sigma_{C-Hax} \rightarrow \pi^*_{C=Y}$, $\pi_{C=Y} \rightarrow \sigma^*_{C-Hax}$, $n_X \rightarrow \sigma^*_{C-Hax}$, $n_{\beta O} \rightarrow \sigma^*_{C-Heq}$, and $\sigma_{S-C} \rightarrow \sigma^*_{C-Heq}$ stereoelectronic effects that is, nevertheless, attenuated by saturation effects. (4) Modulation of the C=Y acceptor character of the exocyclic π group by conjugation with α-heteroatoms O, N, and S in lactones, lactams, and methylidenic analogues **13**−**24** results in decreased $\sigma_{C-Hax} \rightarrow \pi^*_{C=Y}$ and $\pi_{C=Y} \rightarrow \sigma^*_{C-Hax}$ hyperconjugation. (5) Additivity of $\sigma_{C-Hax} \rightarrow \pi^*_{C=Y}$ and $\pi_{C=Y} \rightarrow \sigma^*_{C-Hax}$ hyperconjugative effects is also apparent in 1,3-dicarbonyl derivative **25** (C=Y equal to C=O), 1,3-dithiocarbonyl derivative **26** (C=Y equal to C=S), and 1,3-dimethylidenic analogue **27** (C=Y equal to C=CH_2).

Introduction

The "anomeric effect" (the tendency exhibited by electronegative substituents at the anomeric carbon in pyranose derivatives to adopt the axial rather than the equatorial orientation) is probably, as suggested by E. L. Eliel,[3] the most studied subject in physical organic chemistry since carbocations. The extraordinary interest attracted to the study of the anomeric effect is due to the fact that the fundamental interactions responsible for the unusual conformational behavior seems to be also responsible for the reactivity patterns and stereochemical outcome of many chemical and biochemical reactions.[4]

SCHEME 1



Indeed, as sketched in Scheme 1, both electrostatic dipole−dipole and stereoelectronic interactions ($n_O \rightarrow \sigma^*_{C-Y}$; Y = the electronegative substituent) are involved in the stabilization of the axial conformers.[5−7]

Two-electron/two-orbital hyperconjugative processes, such as the one depicted in Scheme 1, depend on the

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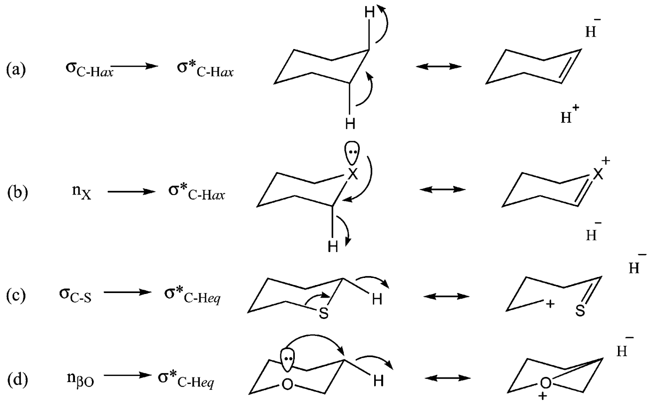
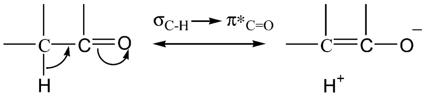
relative orientation between bonds and lone pairs in a molecule and are also inversely proportional to the energy difference between the interacting orbitals. As a consequence, the strongest stabilizing interactions usually take place between the most effective donor (occupied) orbitals and the most effective acceptor (empty) orbitals. Furthermore, the orientation between bonds and lone pairs in a molecule may lead to stereospecific bond cleavage and/or bond formation, which is of fundamental importance in areas such as diastereo- and enantioselective synthesis.

Particularly useful in this field are spectroscopic manifestations of stereoelectronic interactions. Empirical observations together with theoretical interpretations confirm the relevance of $\sigma_{\mathrm{C-H}ax} \rightarrow \sigma^*_{\mathrm{C-H}ax}$,[8] $\mathrm{n_X} \rightarrow \sigma^*_{\mathrm{C-H}ax}$ (X = O or N),[9] $\sigma_{\mathrm{C-S}} \rightarrow \sigma^*_{\mathrm{C-H}eq}$,[10] and $\mathrm{n}_{\beta\mathrm{O}} \rightarrow \sigma^*_{\mathrm{C-H}eq}$[11,12] two-electron/two-orbital stereoelectronic interactions that weaken the acceptor C−H bonds and attenuate the Fermi contribution to the one-bond ^{13}C/^{1}H coupling constants (Scheme 2).

Very recently,[13] theoretical determination [B3LYP/6-31G(*d*,*p*) and PP/IGLO//B3LYP/6-31G(*d*,*p*) methods] of the structural (in particular, C−H bond distances) and spectroscopic (specifically, one-bond $^{1}J_{\mathrm{C-H}}$ NMR coupling constants) consequences of stereoelectronic hyperconjugative effects in cyclohexanone derivatives confirmed the importance of a different form of hyperconjugation in those π systems; in particular, σ C−H bonds can act as electron donors to the adjacent π double bonds of carbonyl groups, as depicted in eq 1.[14]

SCHEME 2





$$-\underset{\mathrm{H}}{\overset{|}{\mathrm{C}}}-\overset{|}{\mathrm{C}}=\mathrm{O} \;\xleftrightarrow{\sigma_{\mathrm{C-H}} \rightarrow \pi^*_{\mathrm{C=O}}}\; -\underset{\mathrm{H^+}}{\overset{|}{\mathrm{C}}}=\overset{|}{\mathrm{C}}-\mathrm{O}^- \qquad (1)$$

In this paper, we describe a computational study aimed at determining the relative importance of hyperconjugative interactions involving σ C−H donor bonds and the carbonyl (C=O), thiocarbonyl (C=S), and methylidene (C=CH$_2$) π systems as the acceptor orbitals. Specifically, we sought the manifestation of $\sigma_{\mathrm{C-H}} \rightarrow \pi^*_{\mathrm{C=Y}}$ (Y = O, S, or CH$_2$) stereoelectronic interactions upon the magnitude of calculated $^{1}J_{\mathrm{C-H}}$ coupling constants, which generally should also correlate with the corresponding C−H bond lengths (i.e., the longer the bond, the weaker the $^{1}J_{\mathrm{C-H}}$ coupling constant). An additional stereoelectronic effect that was evaluated is the alternative $\pi_{\mathrm{C=Y}} \rightarrow \sigma^*_{\mathrm{C-H}ax}$ interaction, where the π orbital is the donor and the σ C−H orbital is the acceptor. This hyperconjugative interaction should also lead to C−H bond elongation and weakening. Also of interest is to confirm whether stereoelectronic effects are additive in systems with two π systems or molecules that include both an acceptor π system and a donor atom (e.g., oxygen or nitrogen) or bond, such as the C−S bond. Such additivity could be anticipated in light of previous observations.[13] Finally, comparison is made of the relative acceptor strength of isolated π systems and those that are part of ester (lactone), amide (lactam), or vinylic ether segments.

Results and Discussion

A. General Remarks. Chart 1 presents the 27 molecular structures that were examined in this work. Cyclohexane **1** and cyclohexanone **2** serve as reference compounds, where the consequences of $\sigma_{\mathrm{C-H}ax} \rightarrow \sigma^*_{\mathrm{C-H}ax}$ and $\sigma_{\mathrm{C-H}ax} \rightarrow \pi^*_{\mathrm{C=O}}$ hyperconjugation on $^{1}J_{\mathrm{C-H}}$ coupling constants have been thoroughly discussed.[13]

Thiocyclohexanone **3** and methylenecyclohexane **4** provide the required information on the relative acceptor ability of the carbonyl (C=O), thiocarbonyl (C=S), and

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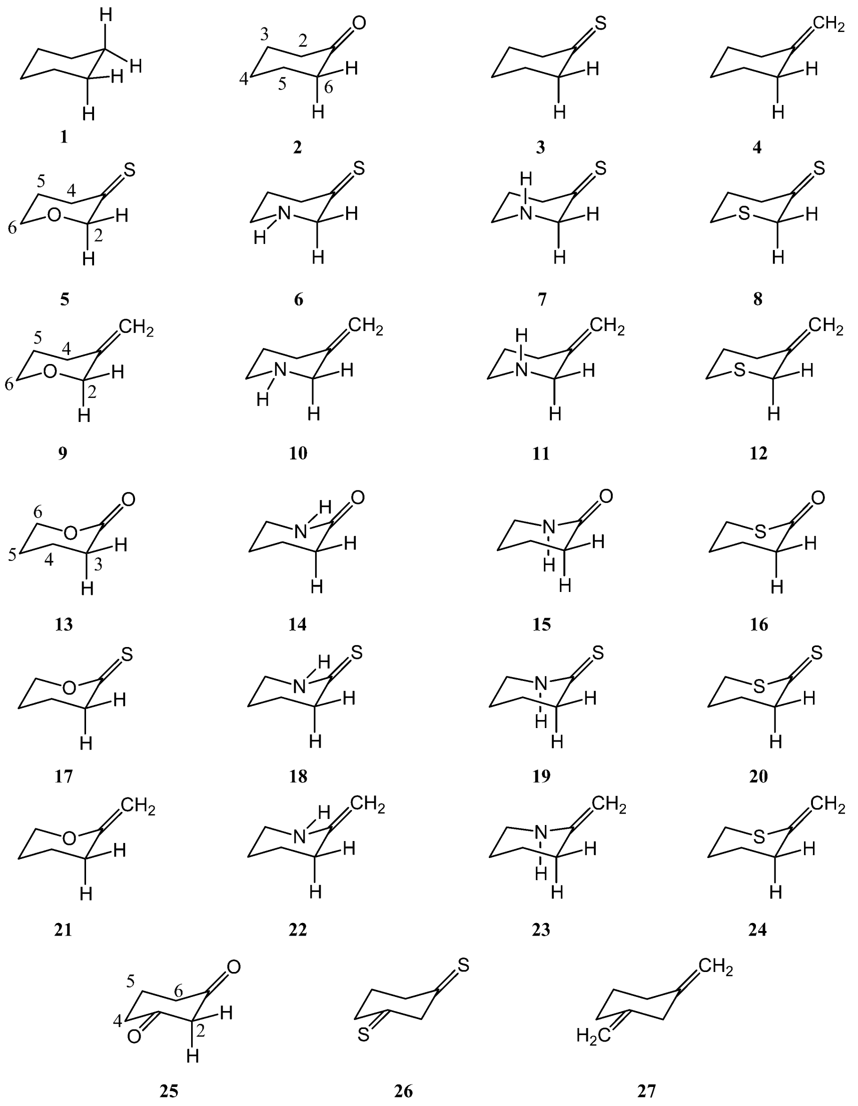
CHART 1



methylidene ($C{=}CH_2$) π systems toward the σ_{C-H} donor orbital. Specifically, $\sigma_{C-H} \rightarrow \pi^*$ hyperconjugation results in longer and weaker C–H bonds that are anticipated to exhibit smaller ${}^1J_{C-H}$ coupling constants.[9–13,15]

Heterocyclic derivatives **5**–**12** present four distinct pairs of methylenic C–H bonds. Most interestingly, the axial C–H bond at C(2) can participate in three stereoelectronic interactions [as a donor in a $\sigma_{C-Hax} \rightarrow \pi^*_{C=Y}$ interaction, as an acceptor in an $n_X \rightarrow \sigma^*_{C-Happ}$ (app = antiperiplanar to the lone pair) "anomeric-type" interaction, and in a $\pi_{C=Y} \rightarrow \sigma^*_{C-Hax}$ hyperconjugation]. None of these interactions should be relevant in C(2)–H_{eq}; so, the difference of ${}^1J_{C(2)-Heq} - {}^1J_{C(2)-Hax}$ should be a measure of the degree of additivity of hyperconjugative mechanisms, which are best evaluated by the examination of C–H_{ax} and C–H_{eq} and C(4), where only the $\sigma_{C-Hax} \rightarrow \pi^*_{C=Y}$ and $\pi_{C=Y} \rightarrow \sigma^*_{C-Hax}$ interactions are relevant, and at C(6), where $n_X \rightarrow \sigma^*_{C-Hax}$ must be the dominant stereoelectronic interaction relative to $\sigma_{C-Heq} \rightarrow \sigma^*_{C-C}$ or $\sigma_{C-Heq} \rightarrow \sigma^*_{X-C}$ alternative interactions that weaken the equatorial C(6)–H bond.[16]

The endocyclic heteroatoms (X = O, N, or S) in compounds **13**–**24** are capable, in principle, of conjugating with the exocyclic double bonds. Such $X{-}C{=}Y \leftrightarrow X^+{=}C{-}Y^-$ conjugation is anticipated to decrease the acceptor character of the π system and should be reflected in an attenuation of the $\sigma_{C-Hax} \rightarrow \pi^*_{C=Y}$ stereoelectronic interaction.

Finally, compounds **25**–**27** can also provide useful data regarding the question of additivity of stereoelectronic effects on C–H bond length and ${}^1J_{C-H}$ coupling constants. Indeed, the methylenic axial and equatorial bonds at C(2) in **25**–**27** are adjacent to two π bonds so that two $\sigma_{C-Hax} \rightarrow \pi^*_{C=Y}$ and $\pi_{C=Y} \rightarrow \sigma^*_{C-Hax}$ interactions are possible. In contrast, the methylenic C–H bonds at C(4,6) in compounds **25**–**27** are both adjacent to one double bond.

Although the rigid geometry of six-membered heterocycles can prevent true antiperiplanar arrangements of the donor and acceptor orbitals, there is ample precedent demonstrating the usefulness of six-membered frameworks in the study of stereoelectronic effects.[3,4,10]

B. Computational Methods. Full geometry optimizations (no symmetry constraints) of all of the compounds

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(15) Nevertheless, exceptions where longer C–H bonds are associated with larger one-bond coupling constants have been recorded.[10e,12a]

(16) It has been established by Alabugin that σ^*_{C-C} and σ^*_{S-C} are rather poor acceptor orbitals.[12a]

were performed using the hybrid functional B3LYP with a 6-31G(d,p) basis set. For all of the compounds, 6 d and 10 f orbital functions were used. These calculations were carried out with the Gaussian 94 program (G94).[17] As reported in this protocol, electron exchange is taken into account by a combined local and gradient-corrected correlation functional, $C{*}^{E_{\mathrm{C}}{}^{\mathrm{LYP}}} + (1 - C){*}^{E_{\mathrm{C}}{}^{\mathrm{VWN}}}$, where LYP is the correlation functional of Lee, Yang, and Parr,[18] including both local and gradient-corrected terms, and VWN is the Vosco, Wilk, and Nusair 1980 correlation functional fitting the RPA solution to the uniform gas, often called the local spin density (LSD) correlation.[19] VWN is used to provide the excess local correlation required since LYP contains a local term essentially equivalent to VWN.[18]

The density functional calculation of ^{1}H and ^{13}C NMR coupling constants was done using the recently proposed approach of Malkin, Malkina, and Salahub.[20−22] Within this methodology, three contributions to the NMR coupling constants are considered, namely, the Fermi contact (FC), the paramagnetic spin−orbit (PSO), and the diamagnetic spin−orbit (DSO). The spin-dipolar (SD) and cross terms such as FC−SD are neglected. The FC term is calculated by the finite perturbation theory (FPT); the PSO contribution is obtained using the sum-over-states density functional perturbation theory (SOS-DFPT),[20a] and the DSO term is determined by numerical integration.[21,22] These spin−spin coupling constant calculations were carried out with a modified version of the deMon KS program[23,24] along with the deMon NMR program.[21−23] Following the suggestions made by the authors of this latter code, we calculated the NMR spin−spin coupling constants using the semilocal exchange of Perdew and Wang[25] and the correlation functional of Perdew,[26] a combination that will be denoted as PP. A value of 0.001 was used for the perturbation parameter in the FPT calculation of the FC term, and the lighter nucleus is selected as the perturbation center. The PSO contribution was obtained with the local one approximation.[20] A fine grid (with 32 radial points) with an extra iteration was used, and the basis set employed in the coupling constant calculations was the IGLO-III of Kutzelnigg.[27] Thus, as we follow the usual notation, the level of theory for the determination of coupling constants used in this work is PP/IGLO-III//B3LYP/6-31G(d,p).

NBO analyses were performed with version 3.1 (included in G94),[28] and this was used to evaluate changes in hyperconjugation. The interactions between filled and vacant orbitals represent the deviation of the molecule from the Lewis structure and can be used as a measurement of delocalization.[29]

C. Cyclohexane 1, Cyclohexanone 2, Thiocyclohexanone 3, and Methylenecyclohexane 4. Table 1 of the Supporting Information collects the structural data for the title compounds **1**−**4**. As discussed previously,[10b,12a,13] the slightly longer (and thus weaker) axial C−H bond in cyclohexane (C−H$_{ax}$ = 1.100 Å versus C−H$_{eq}$ = 1.098 Å, Table 1 of the Supporting Information) is the result of $\sigma_{\mathrm{C-H}ax} \rightarrow \sigma^*_{\mathrm{C-H}ax}$ hyperconjugation between antiperiplanar bonds.

A salient observation in Table 1 of the Supporting Information is the significant difference in Z−C(2) bond lengths. Indeed, the Z−C(2) bond length in cyclohexanone **2** is significantly longer than those of its congeners **3** and **4**. These differences are important in describing the contrasting hyperconjugative effects in these systems, as discussed below.

Although the bond length difference between axial and equatorial C−H bonds in cyclohexane is small ($r_{\mathrm{C-H}ax} - r_{\mathrm{C-H}eq}$ = 0.002 Å), it becomes quite large for methylenes adjacent to the carbonyl group in cyclohexanone **2** ($r_{\mathrm{C(2)-H}ax} - r_{\mathrm{C(2)-H}eq}$ = 1.100 − 1.093 = 0.007 Å, Table 1 of the Supporting Information). Surprisingly, the bond length difference in methylenic C−H bonds that are adjacent to the thiocarbonyl group in thiocyclohexanone **3** is calculated to be even larger ($r_{\mathrm{C(2)-H}ax} - r_{\mathrm{C(2)-H}eq}$ = 1.101 − 1.092 = 0.009 Å, Table 1 of the Supporting Information). By contrast, $\Delta r_{\mathrm{C-H}ax,eq}$ for the methylenes adjacent to the C═CH$_2$ methylidene group in **4** is smaller than that observed in cyclohexanone **2** (0.006 and 0.007 Å, respectively).

Interestingly, and contrary to our initial expectation, the larger differences between axial and equatorial C(2)−H bond lengths in compounds **2**−**4** relative to cyclohexane **1** cannot be ascribed solely to a lengthening of the axial C−H bonds as a result of the $\sigma_{\mathrm{C(2)-H}ax} \rightarrow \pi^*_{\mathrm{C=Y}}$ stereoelectronic interaction present in the unsaturated models[13] since the data reported in Table 1 (Supporting Information) clearly show that the axial C(2)−H bond lengths do not change significantly and the differences actually result from the variations in the equatorial C(2)−H bonds. In particular, the C(2)−H$_{eq}$ bond distance is shortest (1.092 Å) in thioketone **3**, followed by ketone **2** (1.093 Å) and methylenecyclohexane **4** (1.095 Å). By comparison, the calculated C(2)−H$_{eq}$ bond length in the reference cyclohexane is a "normal" 1.098 Å.

What makes the C−H$_{eq}$ bonds stronger in **2**−**4**? A reasonable interpretation can be advanced in terms of

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SCHEME 3

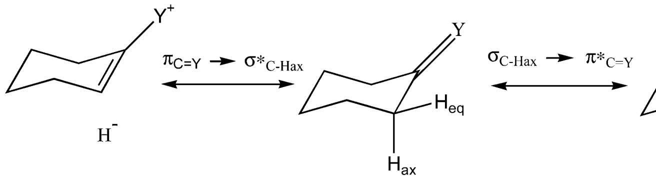
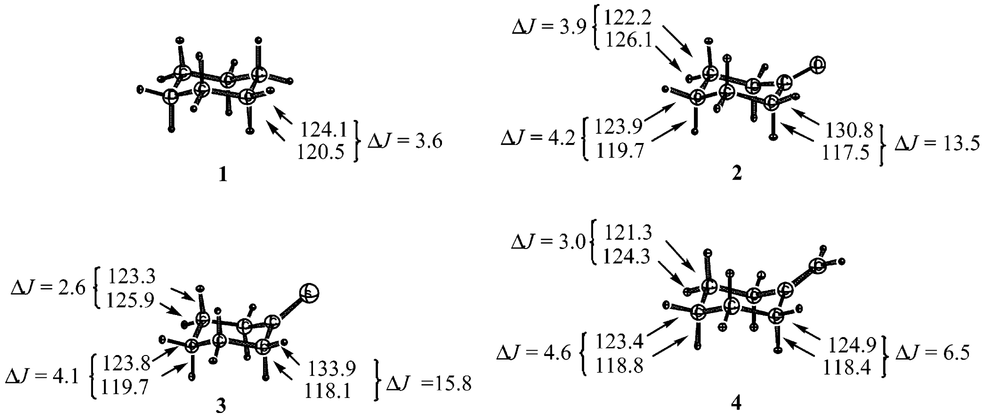


CHART 2



the double bond−no bond canonical structure that originates from $\sigma_{C-Hax} \rightarrow \pi^*_{C=Y}$ and $\pi_{C=Y} \rightarrow \sigma^*_{C-Hax}$ hyperconjugative interactions (Scheme 3). Thus, the increased s character in the equatorial C_{sp2}−H bonds renders those bonds stronger (and shorter).

The structural data presented in Table 1 of the Supporting Information and, in particular, the differences in bond lengths between axial and equatorial C(2)−H bonds suggest that $\sigma_{C-Hax} \rightarrow \pi^*_{C=Y}$ and/or $\pi_{C=Y} \rightarrow \sigma^*_{C-Hax}$ hyperconjugation (Scheme 3) is most effective with the thiocarbonyl group, followed by the carbonyl and, finally, the methylidene group.

The above conclusion is supported by the analysis of the corresponding one-bond coupling constants (in hertz, Chart 2). This chart also includes the difference $\Delta J_{ax/eq} = J_{C-Heq} - J_{C-Hax}$ for each distinct methylene in the molecule. Positive ΔJ values reflect typical situations (see Introduction) where $\sigma_{C-Hax} \rightarrow \sigma^*_{C-Hax}$, $n_X \rightarrow \sigma^*_{C-Happ}$, and/or $\sigma_{C-Hax} \rightarrow \pi^*_{C=Y}$ stereoelectronic interactions lead to weaker axial C−H bonds with smaller ${}^1J_{C-Hax}$ coupling constants relative to ${}^1J_{C-Heq}$.[9,10,12,13,30]

Most relevant is that the calculated difference ($\Delta J_{ax/eq}$) for the methylenic C(2,6)−H bonds adjacent to the exocyclic C═Y bonds (Chart 2) decreases in the sequence thioketone **3** ($\Delta J_{ax/eq} = 15.8$ Hz) > ketone **2** ($\Delta J_{ax/eq} = 13.5$ Hz) > methylenecyclohexane **4** ($\Delta J_{ax/eq} = 6.5$ Hz), which is, nevertheless, larger than $\Delta J_{ax/eq} = 3.6$ Hz that is found in the reference compound cyclohexane **1**. This trend is, of course, in line with the structural evidence reported in Table 1 (Supporting Information) and discussed above that indicates that the relative acceptor ability of the π bonds diminishes in the order C═S > C═O > C═CH$_2$. 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 (eq 1). Simultaneously, the potential role of $\pi_{C=Y} \rightarrow \sigma^*_{C-Hax}$ hyperconjugation must be considered, as discussed in the Introduction.

As was recently shown by Alabugin,[12] the natural bond orbitals (NBO) method developed by Weinhold and coworkers is a very useful theoretical method for the study of hyperconjugative interactions.[29,31] 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 corresponding Fock elements and followed by the recalculation of the wave function.[12a]

Table 1 summarizes the NBO-estimated energies of deletion (E_{del}) for the main hyperconjugative interactions in cyclohexanone **2**, thiocyclohexanone **3**, and methylenecyclohexane **4**. 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 **3** ($\Delta E = 0.45$ hartree) results in a stronger delocalizing interaction $\sigma_{C(2,6)-Hax} \rightarrow \pi^*_{C=S}$ ($E_{del} = 7.32$ kcal/mol) relative to the corresponding stereoelectronic interaction in cyclohexanone **2** ($E_{del} = 5.47$ kcal/mol for $\sigma_{C(2,6)-Hax} \rightarrow \pi^*_{C=O}$). By the same token, the donor ($\sigma_{C(2,6)-Hax}$) to acceptor ($\pi^*_{C=CH_2}$) energy gap in methylenecyclohexane **4** is largest ($\Delta E = 0.55$ hartree), and this is manifested in weaker $\sigma_{C-Hax} \rightarrow \pi^*_{C=CH_2}$ hyperconjugation. Unexpectedly, the E_{del} value calculated for $\sigma_{C(2,6)-Hax} \rightarrow \pi^*_{C=CH_2}$ hyperconjugation in **4** is slightly larger than the corresponding value in

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[30] (a) Freeman, F.; Phornvoranunt, A.; Hehre, W. J. *J. Phys. Org. Chem*. **1998**, *11*, 831. (b) Freeman, F.; Hehre, W. J. *J. Mol. Struct.* (*THEOCHEM*) **2000**, *529*, 225.

[31] (a) Reed, A. E.; Weinhold, F. *J. Chem. Phys*. **1985**, *83*, 1736. (b) Weinhold, F. Natural Bond Orbital Methods. In *Encyclopedia of Computational Chemistry*; Schleyer, P. v. R., Allinger, N. L., Clark, T., Gasteiger, J., Kollman, P. A., Schaefer, H. F., III, Schreiner, P. R., Eds.; John Wiley & Sons: Chichester, U.K., 1998; Vol. III, pp 1792−1811.

SCHEME 4

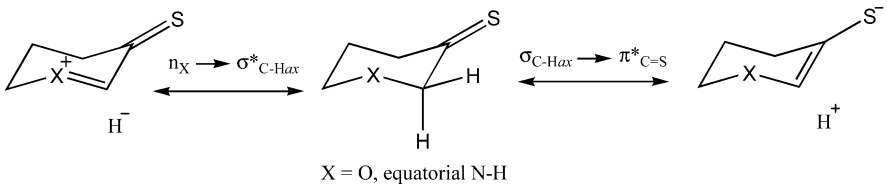
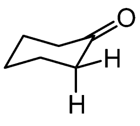
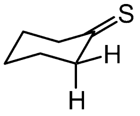
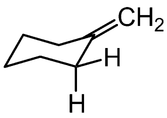


TABLE 1. Selected Hyperconjugative Interactions (E_{del}) for C(2,6)−H Bonds Adjacent to the C═Y Acceptor Group in Cyclohexanone 2, Thiocyclohexanone 3, and Methylenecyclohexane 4

	donor orbital	acceptor orbital	E_{del} (kcal/mol)	ΔE donor/acceptor (Hartrees)
 **2**	$\sigma_{C(2,6)\text{-}Hax}$	$\sigma^*_{C\text{-}O}$	1.195	1.11
	$\sigma_{C(2,6)\text{-}Hax}$	$\pi^*_{C=O}$	5.474	0.53
	$\sigma_{C(2,6)\text{-}Heq}$	$\sigma^*_{C\text{-}O}$	1.243	1.11
	$\sigma_{C(2,6)\text{-}Heq}$	$\pi^*_{C=O}$	0.054	0.53
	$\sigma_{C\text{-}O}$	$\sigma^*_{C(2,6)\text{-}Hax}$	-0.32	1.51
	$\pi_{C=O}$	$\sigma^*_{C(2,6)\text{-}Hax}$	2.46	0.80
 **3**	$\sigma_{C(2,6)\text{-}Hax}$	$\sigma^*_{C\text{-}S}$	2.28	0.82
	$\sigma_{C(2,6)\text{-}Hax}$	$\pi^*_{C=S}$	7.32	0.45
	$\sigma_{C(2,6)\text{-}Heq}$	$\sigma^*_{C\text{-}S}$	0.05	--
	$\sigma_{C(2,6)\text{-}Heq}$	$\pi^*_{C=S}$	0.00	--
	$\sigma_{C\text{-}S}$	$\sigma^*_{C(2,6)\text{-}Hax}$	0.762	1.17
	$\pi_{C=S}$	$\sigma^*_{C(2,6)\text{-}Hax}$	3.53	0.7
 **4**	$\sigma_{C(2,6)\text{-}Hax}$	$\sigma^*_{C\text{-}C}$	1.615	1.16
	$\sigma_{C(2,6)\text{-}Hax}$	$\pi^*_{C=C}$	5.790	0.55
	$\sigma_{C(2,6)\text{-}Heq}$	$\sigma^*_{C\text{-}C}$	0.119	--
	$\sigma_{C(2,6)\text{-}Heq}$	$\pi^*_{C=C}$	0.015	--
	$\sigma_{C\text{-}CH2}$	$\sigma^*_{C(2,6)\text{-}Hax}$	0.44	1.17
	$\pi_{C=CH2}$	$\sigma^*_{C(2,6)\text{-}Hax}$	4.86	0.70

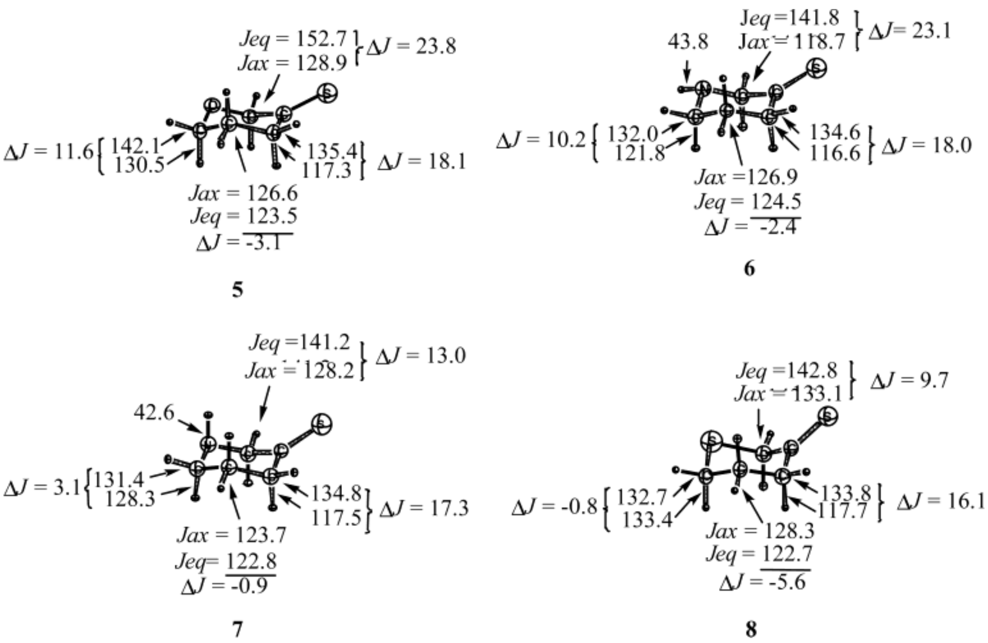
cyclohexanone **2** (5.790 versus 5.474 kcal/mol, respectively, Table 1), but this observation can probably be interpreted as a consequence of the substantially shorter C(2)−C═CH_2 bond length relative to the C(2)−C═O bond length (1.513 and 1.543 Å, respectively, Table 1 of the Supporting Information) that results in better donor/acceptor orbital overlap in **4**.

With regard the relative importance of $\sigma_{C-Hax} \rightarrow \pi^*_{C=Y}$ and $\pi_{C=Y} \rightarrow \sigma^*_{C-Hax}$ hyperconjugation, E_{del} values for the former are substantially larger, except in the case of the methylidenic segment, where the lower electronegativity of Y = CH_2 renders the corresponding π orbital a relatively better donor.

One obvious consequence of the more relevant $\sigma_{C-Hax} \rightarrow \pi^*_{C=S}$ hyperconjugation mechanism relative to that of $\sigma_{C-Hax} \rightarrow \pi^*_{C=O}$ is that thioketones must be more acidic than the corresponding ketones. Although the extensive acidity (pK_a) listings of Streitwieser et al.[32a] and Bordwell[32b] do not include values for thioketones, we note that thioacetamide is seven pK_a units more acidic than acetamide.[32b] Another argument is that the enol/keto ratio is greater for thioketones, and the thioenoles are more acidic than enols;[33] therefore, the thioketones are also more acidic.

With regard to methylenic C−H_{ax} and C−H_{eq} at C(3,5) and C(4), the small differences in $^1J_{C-Hax} - {}^1J_{C-Heq} = 2.6-4.6$ Hz are similar within the ±1.0 Hz margin of error to $\Delta J_{ax/eq}$ values observed in cyclohexane **1** (Table 1 of the Supporting Information) and suggest that the main

CHART 3



stereoelectronic interaction taking place corresponds to $\sigma_{\mathrm{C-H}ax} \rightarrow \sigma^*_{\mathrm{C-H}ax}$, which results in weaker axial C−H bonds.

D. 1-Heterocyclohexane-3-thiones 5−8. Table 3 of the Supporting Information collects the calculated structural data for thioketones **5**−**8**, where the axial and equatorial C(2)−H bonds provide convenient probes for potentially additive $\sigma_{\mathrm{C-H}ax} \rightarrow \pi^*_{\mathrm{C=S}}$, $\pi_{\mathrm{C=S}} \rightarrow \sigma^*_{\mathrm{C-H}ax}$, and $n_X \rightarrow \sigma^*_{\mathrm{C-H}ax}$ hyperconjugative interactions.

Most interesting is that a very large difference in bond lengths (Δr) is calculated for the axial vis-à-vis equatorial C−H bonds adjacent to both the thiocarbonyl group and oxygen in **5** or equatorial N−H in compound **6**. Indeed, $\Delta r_{ax/eq}$ values at C(2) in heterocyclic thioketones **5** and **6** are estimated as 1.108 − 1.090 = 0.018 Å and 1.112 − 1.091 = 0.021 Å, respectively. This dramatic observation supports the additive effect of $\sigma_{\mathrm{C-H}ax} \rightarrow \pi^*_{\mathrm{C=S}}$, $\pi_{\mathrm{C=S}} \rightarrow \sigma^*_{\mathrm{C-H}ax}$, and either $n_O \rightarrow \sigma^*_{\mathrm{C-H}ax}$ in oxacyclohexane-thione **5** or $n_N \rightarrow \sigma^*_{\mathrm{C-H}ax}$ hyperconjugation in azacyclohexane-thione **6**, as discussed in the Introduction (Scheme 4).

By comparison, $\Delta r_{ax/eq}$ values at C(2) in heterocycles **7** (X = axial N−H, $\Delta r_{ax/eq}$ = 1.101 − 1.092 = 0.009 Å) and **8** (X = S, $\Delta r_{ax/eq}$ = 1.098 − 1.090 = 0.008 Å) are about one-half of those encountered in **5** and **6** and are in line with those expected; in aza derivative **7**, the axial orientation of the N−H bond prevents $n_N \rightarrow \sigma^*_{\mathrm{C(2)-H}ax}$ hyperconjugation, whereas in thiocyclohexane thione **8**, the lone pairs on sulfur (n_S) are not efficient in $n_S \rightarrow \sigma^*_{\mathrm{C(2)-H}ax}$ hyperconjugation.[10,34] Under these circumstances, mainly one stereoelectronic interaction is operative, $\sigma_{\mathrm{C(2)-H}ax} \rightarrow \pi^*_{\mathrm{C=S}}$, which is manifested in the increased length of the axial C(2)−H bonds.

According to the same argument, at C(4) in **5**−**8**, the axial C−H bonds participate in $\sigma_{\mathrm{C-H}ax} \rightarrow \pi^*_{\mathrm{C=Y}}$ and $\pi_{\mathrm{C=Y}} \rightarrow \sigma^*_{\mathrm{C-H}ax}$ hyperconjugation, and this is reflected in their increased bond length relative to the equatorial C(4)−H$_{eq}$ bonds. Indeed, $\Delta r_{ax/eq}$ is a nearly identical 0.010 Å in all four thiones **5**−**8** (Table 3 of the Supporting Information).

By contrast, $\Delta r_{ax/eq}$ for the methylenic C−H bonds at C(5) in derivatives **5** and **6** is equal to zero (Table 3 of the Supporting Information). This result suggests that the "cyclohexane-like" $\sigma_{\mathrm{C-H}ax} \rightarrow \sigma^*_{\mathrm{C-H}ax}$ stereoelectronic interaction that is expected to result in slightly longer C−H$_{ax}$ bonds (see Introduction) is balanced by the through-space $n_{\beta O} \rightarrow \sigma^*_{\mathrm{C-H}eq}$ stereoelectronic interaction that should lengthen the equatorial C−H bond (see Introduction). Furthermore, the equatorial C(5)−H bond in thione **8** is actually slightly longer than the corresponding axial C−H bond ($\Delta r_{ax/eq}$ = 1.095 − 1.097 = −0.002 Å, Table 3 of the Supporting Information), and this observation is in line with a dominant $\sigma_{\mathrm{S-C}} \rightarrow \sigma^*_{\mathrm{C(5)-H}eq}$ hyperconjugative interaction that results in a longer equatorial C−H bond. By comparison, an analogous $\sigma_{\mathrm{N-C}} \rightarrow \sigma^*_{\mathrm{C(5)-H}eq}$ interaction in azathione **7** appears to be less efficient, $\Delta r_{ax/eq}$ = 1.098 − 1.097 = 0.001 Å. (Table 3 of the Supporting Information).

With regard to the methylenic C−H bonds at C(6) in **5** and **6**, $n_X \rightarrow \sigma^*_{\mathrm{C-H}ax}$ (X = O, equatorial N−H) hyperconjugation makes the axial C(6)−H bonds longer than the corresponding equatorial C(6)−H bonds: $\Delta r_{ax/eq}$ = 0.011 and 0.014 Å, respectively. By contrast, the slightly longer C(6)−H$_{ax}$ bonds in **7** and **8** are explained in terms of exclusive $\sigma_{\mathrm{C-H}ax} \rightarrow \sigma^*_{\mathrm{C-H}ax}$ interactions.

The arguments presented above in terms of calculated bond lengths are supported by the analysis of the relative magnitude of $^1J_{\mathrm{C-H}}$ coupling constants calculated for 1-heterocyclohexane-3-thiones **5**−**8**, which are collected in Chart 3 and which are usually a direct consequence of the corresponding C−H bond lengths. Indeed, $\Delta J_{ax/eq}$ ($^1J_{\mathrm{C-H}ax} - {}^1J_{\mathrm{C-H}eq}$) is largest for C(2) in thiones **5** and **6**

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(32) (a) Streitwieser, A., Jr.; Juaristi, E.; Nebenzahl, L. L. In *Comprehensive Carbanion Chemistry*; Buncel, E., Durst, T., Eds.; Elsevier: Amsterdam, The Netherlands, 1980; Chapter 7. (b) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.

(33) (a) Apeloig, Y. In *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley: New York, 1990; Chapter 1, p 45. (b) Zhang, X.-M.; Malick, D.; Petersson, G. A. *J. Org. Chem.* **1998**, *63*, 5314.

(34) Anet, F. A. L.; Kopelevich, M. *J. Chem. Soc., Chem. Commun.* **1987**, 595.

(23.8 and 23.1 Hz, respectively) and is mainly due to the combined $n_X \rightarrow \sigma^*_{C(2)-Hax}$ and $\sigma_{C-Hax} \rightarrow \pi^*_{C=S}$ hyperconjugative interactions that weaken the axial C−H bond relative to the equatorial C−H bond. By contrast, $\Delta J_{ax/eq}$ at C(4) in **5** and **6** is 18.1 and 18.0 Hz, respectively, which now reflects almost exclusively the effect of $\sigma_{C(4)-Hax} \rightarrow \pi^*_{C=S}$ and $\pi_{C=S} \rightarrow \sigma^*_{C-Hax}$ hyperconjugation. By the same token, $\Delta J_{ax/eq}$ values at C(6) in these compounds (11.6 and 10.2 Hz, respectively) arise from a dominant stereoelectronic effect, namely, $n_X \rightarrow \sigma^*_{C(6)-Hax}$. Interestingly, $\Delta J_{ax/eq}$ values at C(5) in **5** and **6** are negative (−3.1 and −2.4 Hz, respectively). The smaller one-bond coupling constants in these compounds originate from the through-space $n_{\beta O} \rightarrow \sigma^*_{C(5)-Heq}$ hyperconjugative interaction that weakens the equatorial C−H bonds.

Also quite informative is the comparison of azacyclohexane-thiones **6** (equatorial N−H) and **7** (axial N−H). At C(2), the consequence of "turning off" the anomeric-type $n_N \rightarrow \sigma^*_{C(2)-Hax}$ hyperconjugative interaction in **7** brings about a decrease in $\Delta J_{ax/eq}$ since now only the $\sigma_{C(2)-Hax} \rightarrow \pi^*_{C=S}$ and $\pi_{C=S} \rightarrow \sigma^*_{C-Hax}$ interactions are operative. No change is introduced at C(4) upon nitrogen inversion ($\Delta J_{ax/eq} = 18.0$ Hz in **6**, $\Delta J_{ax/eq} = 17.3$ Hz in **7**), but the negative $\Delta J_{ax/eq}$ at C(5) decreases in magnitude ($\Delta J_{ax/eq} = -2.4$ Hz in **6**, $\Delta J_{ax/eq} = -0.9$ Hz in **7**) since $n_{\beta N} \rightarrow \sigma^*_{C(5)-Heq}$ is now less important.[12b] Finally, at C(6), one observes that the sizable value of $\Delta J_{ax/eq} = 10.2$ Hz that is measured in **6** decreases to $\Delta J_{ax/eq} = 3.1$ Hz in **7** since the $n_N \rightarrow \sigma^*_{C(6)-Hax}$ that operates in **6** becomes ineffective in **7**, where the nitrogen lone pair is no longer antiperiplanar to the axial C−H bond (Chart 3).

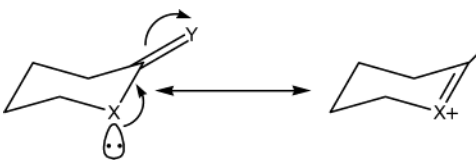
In the case of thiacyclohexane-thione **8**, where the ring sulfur is ineffective in the $n_S \rightarrow \sigma^*_{C-Hax}$ anomeric-type hyperconjugation,[10,34] one finds the anticipated (see the discussion for **7** above) decrease in $\Delta J_{ax/eq}$ values at C(2) and C(4), as compared to those with **5** and **6**. By contrast, the substantially negative $\Delta J_{ax/eq} = -5.6$ Hz encountered at C(5) can be explained in terms of the $\sigma_{S-C} \rightarrow \sigma^*_{C(5)-Heq}$ stereoelectronic interaction that weakens the equatorial C−H bond.[10] Interestingly, $\Delta J_{ax/eq}$ at C(6) is also negative but smaller in magnitude (−0.8 Hz), suggesting that electron transfer from an antiperiplanar S−C bond orbital is more efficient than that from a C−S donor orbital. That is, as suggested in refs 10c,e and 13, although the energy of the σ_{S-C} and σ_{C-S} orbitals is expected to be the same, bond polarities are actually opposite and this may result in a more efficient $\sigma_{S-C} \rightarrow \sigma^*_{C-Happ}$ interaction relative to $\sigma_{C-S} \rightarrow \sigma^*_{C-Happ}$. Different acceptor abilities of S−C versus C−S orbitals have also been observed by Alabugin and Zeidan,[35] who suggested that the difference in orbital overlap is responsible for the contrasting behavior. Of course, additional hyperconjugative effects weakening the axial and equatorial C(5)−H and C(6)−H bonds in thiacyclohexane-thione **8** should modulate the final values for $\Delta J_{ax/eq}$ that are collected in Chart 3.

E. Methylidene Derivatives 9−12. Table 4 of the Supporting Information shows the calculated structural data for heterocyclic derivatives **9**−**12** that allow for the examination of the relative importance of stereoelectronic interactions involving the heteroatom (e.g., $n_X \rightarrow \sigma^*_{C-Hax}$, $\sigma_{C-X} \rightarrow \sigma^*_{C-Heq}$, $n_{\beta X} \rightarrow \sigma^*_{C-Heq}$) and/or the π system (in particular, in $\sigma_{C-Hax} \rightarrow \pi^*_{C=Y}$ and $\pi_{C=Y} \rightarrow \sigma^*_{C-Hax}$ interactions).

The differences in C−H bond lengths calculated for all methylenes in compounds **9**−**12** follow the same trends observed in thiocarbonyl analogues **5**−**8**, which were discussed in full detail in the previous section. Of course, the corresponding $\Delta r_{ax/eq}$ values in **9**−**12** are attenuated by the fact that the methylidene C═CH$_2$ bond is a weaker acceptor than the thiocarbonyl C═S bond (see section C). For instance, $\Delta r_{ax/eq}$ for the C(2)−H bonds in oxacyclohexane derivative **9** is estimated to be $1.106 - 1.093 = 0.013$ Å (Table 4 of the Supporting Information), whereas the corresponding $\Delta r_{ax/eq}$ for the same C(2) methylene in the thioketone analogue **5** is $1.108 - 1.090 = 0.018$ Å (Table 3 of the Supporting Information). In the latter compound, the larger difference in bond lengths arises from the more relevant $\sigma_{C(2)-Hax} \rightarrow \pi^*_{C=S}$ hyperconjugative interaction, relative to the less-effective $\sigma_{C(2)-Hax} \rightarrow \pi^*_{C=CH_2}$ interaction in **9**. Similarly, $\Delta r_{ax/eq}$ at C(4) in **9** is $1.101 - 1.095 = 0.006$ Å (Table 4 of the Supporting Information), mostly as the consequence of $\sigma_{C(4)-Hax} \rightarrow \pi^*_{C=CH_2}$ hyperconjugation, to be compared with $\Delta r_{ax/eq}$ at C(4) in **5** [$1.102 - 1.092 = 0.010$ Å (Table 3 of the Supporting Information)], where the dominant stereoelectronic interaction corresponds to $\sigma_{C(4)-Hax} \rightarrow \pi^*_{C=S}$.

The rest of the data reported in Table 4 of the Supporting Information is in full agreement with the operation of $\sigma_{C-Hax} \rightarrow \sigma^*_{C-Hax}$, $n_X \rightarrow \sigma^*_{C-Hax}$, $\sigma_{C-X} \rightarrow \sigma^*_{C-Heq}$, and $n_{\beta X} \rightarrow \sigma^*_{C-Heq}$ stereoelectonic interactions that are responsible for C−H bond lengthening, as detailed in section D. Furthermore, the differences in methylenic C−H bond lengths are also reflected in the corresponding differences in one-bond C−H coupling constants collected in Chart 4.

F. α-Heterocyclohexanones 13−16, α-Heterocyclohexanethiones 17−20, and Methylidene Analogues 21−24. 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 $\sigma_{C-Hax} \rightarrow \pi^*_{C=Y}$ stereoelectronic interaction that is operative in compounds **2**−**12**. Specifically, it is anticipated that classical conjugation in the X−C═Y segment will raise the energy of the LUMO π^* orbital, making it a less-efficient acceptor (eq 2).



(2)

Efficient conjugation, as depicted in eq 2, should then attenuate the $\sigma_{C-Hax} \rightarrow \pi^*_{C=Y}$ hyperconjugative interaction already verified in **2**−**12** and should be manifested on the corresponding bond lengths and one-bond coupling constants in six-membered lactones, lactams, and methylidene analogues **13**−**24**. Tables 5−7 of the Supporting Information and Charts 5−7 collect the calculated structural and spectroscopic ($^1J_{C-H}$) data of interest.

There is a wealth of structural data collected in Tables 5−7 of the Supporting Information, but perhaps the most salient observation is the dramatic difference in X−C(2)

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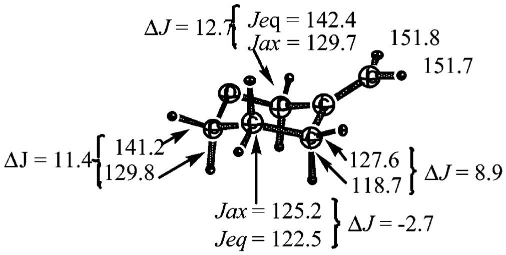
(35) Alabugin, I. V.; Zeidan, T. A. *J. Am. Chem. Soc.* **2002**, *124*, 3175.

CHART 4



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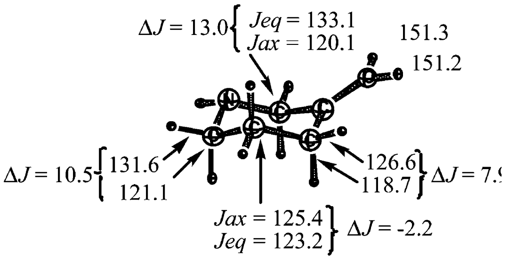

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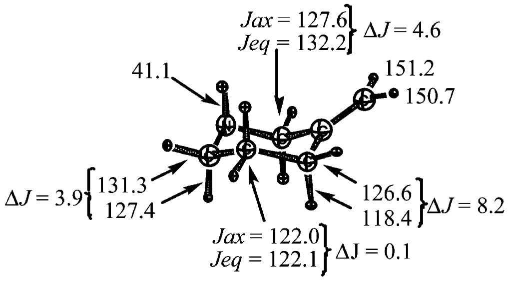

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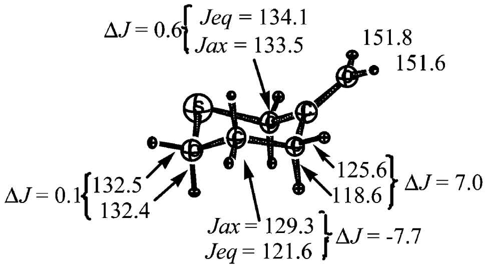

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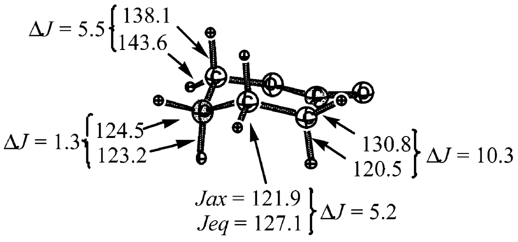
CHART 5



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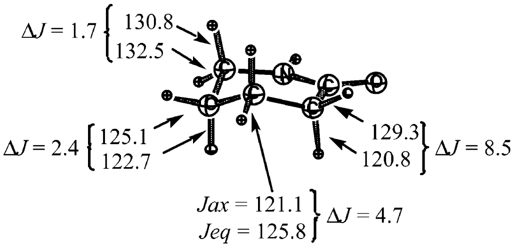

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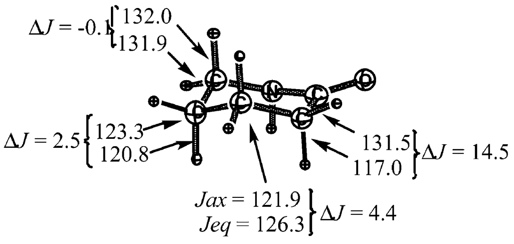

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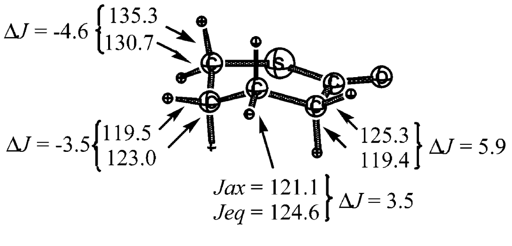


16

bond lengths in systems where $X-C(2)=Y \leftrightarrow X^+=C(2)-Y^-$ conjugation is operative, relative to analogues where conjugation is prevented. Specifically, the $X-C(2)=O$ bond lengths in lactone **13** and lactam **14** (pseudoequatorial N−H) are rather short (1.361 and 1.372 Å, respectively, Table 5 of the Supporting Information) as a consequence of conjugation. By contrast, the N−C(2) bond in lactam **15** (axial N−H) is 1.439 Å long, which is a normal length for an isolated N−C bond. Indeed, the nitrogen lone pair in lactam **15** is not suitably disposed for conjugation with the carbonyl group.

This same tendency [short X−C(2) bonds in conjugated systems and normal X−C(2) bonds in analogues where the axial orientation of the N−H bond prevents resonance] is found in thiocarbonyl derivatives **17**−**20** (Table 6 of the Supporting Information) and methylidene analogues **21**−**24** (Table 7 of the Supporting Information).

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 ${}^1J_{C(3)-Hax}$ coupling constants, and smaller $\Delta^1J_{ax/eq}$ values at C(3)].

Indeed, Chart 5 shows $\Delta^1J_{ax/eq}$ values for the methylenic C−H bonds at C(3) in compounds **13**, **14**, and **16** (10.3, 8.5, and 5.9 Hz, respectively), which are signifi-

CHART 6

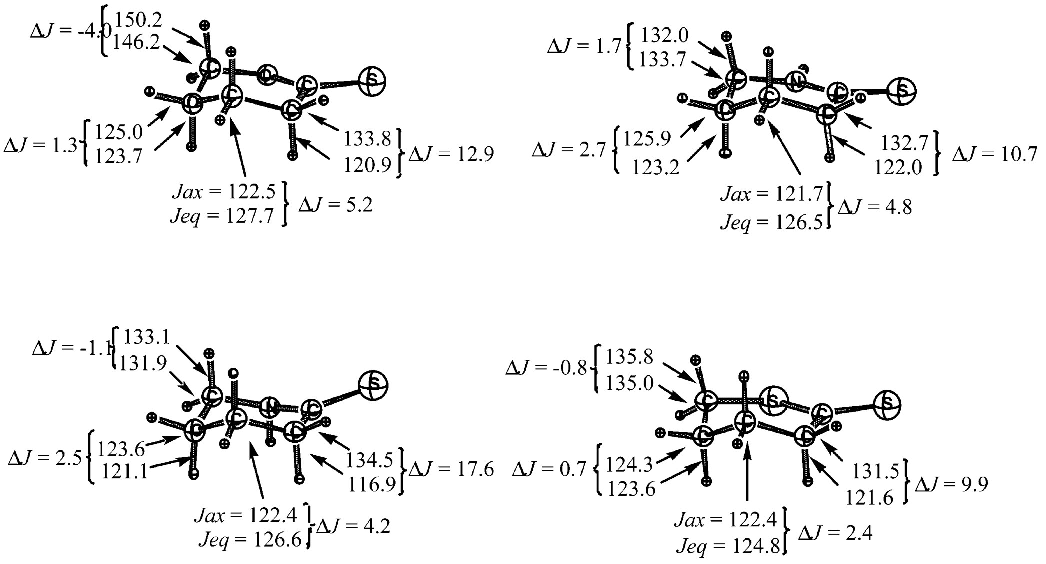
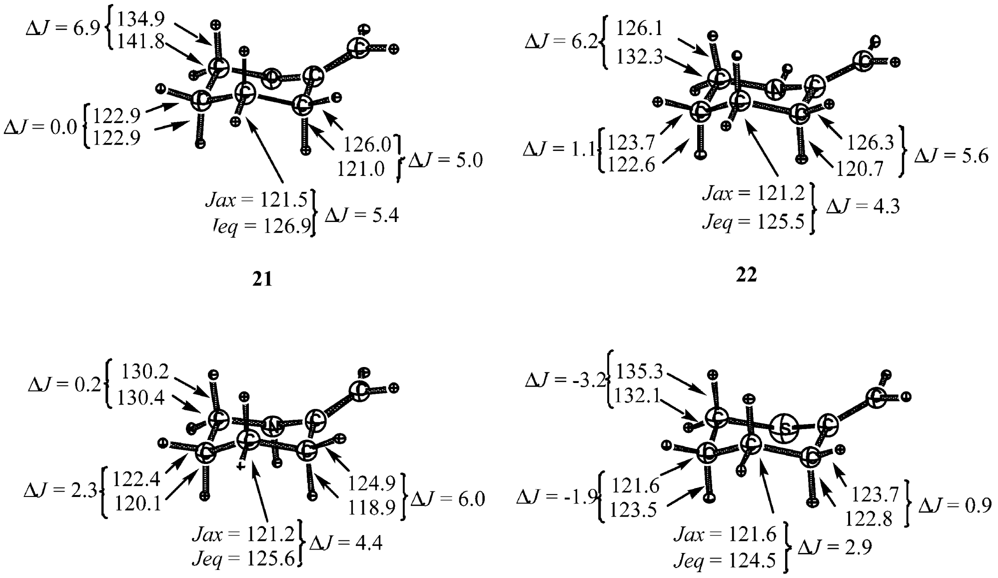


CHART 7



21 **22**

23 **24**

cantly smaller than the corresponding $\Delta^1J_{ax/eq}$ value in the reference cyclohexanone **2** (13.5 Hz, Chart 2). By contrast, lactam **15** shows $\Delta^1J_{ax/eq} = 14.5$ Hz for C(3), and this value is essentially similar to that encountered in **2**. It is then appreciated that the lack of N−C═O conjugation in **15** renders a carbonyl acceptor orbital that is fully active as an acceptor orbital to the C(3)−H_{ax} donor orbital.

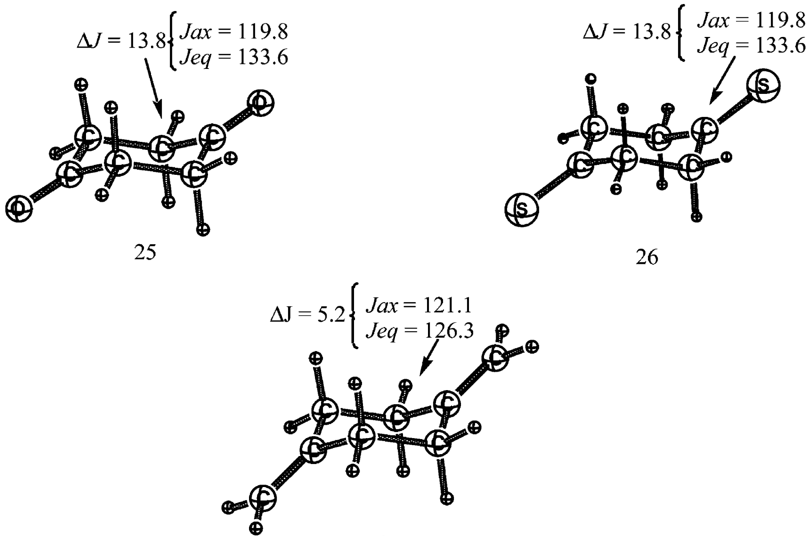
By the same token, $\Delta^1J_{ax/eq}$ for the methylenic C(3)−H bonds in thiocarbonyl derivatives **17**, **18**, and **20** are smaller than the corresponding value difference in thiocyclohexanone **3** (12.9, 10.7, and 9.9 Hz, respectively, versus 15.8 Hz, Charts 2 and 6), whereas $\Delta^1J_{ax/eq} = 17.6$ Hz in thiolactam **19**, where no N−C═S ↔ N^+═C−$^-$S electron delocalization takes place.

Finally, $\Delta^1J_{ax/eq} = 6.5$ Hz for the methylenic C−H bonds adjacent to the C═CH_2 group in the reference methylenecyclohexane **4** (Chart 2). The lower acceptor character of the π orbital in derivatives **21**, **22**, and **24** is reflected in smaller $\Delta^1J_{ax/eq}$ values (5.0, 5.6, and 0.9 Hz, respectively, Chart 7). Again, $\Delta^1J_{ax/eq}$ for C(3) in nonconjugated analogue **23** is larger (6.0 Hz), which is quite similar to the value exhibited by the reference compound **4**. Of course, because of the distorted geometries present in **21**−**24** (Chart 7), the above comparisons and conclusions must be considered with caution.

On the other hand, "anomalous" values for $\Delta^1J_{ax/eq}$ are seen for the methylenic C−H bonds at C(6) (i.e., adjacent to the heteroatom X in **13**−**24**). The rather small (or actually negative) values probably arise from the particular structural arrangement in the CH_2−X−C═Y segment that results in unusual orientations of the C(6)−H bonds (Charts 5−7).

G. Is There Additivity of the $\sigma_{C-H} \rightarrow \pi^*_{C=Y}$ Hyperconjugative Interaction? Table 8 of the Supporting Information and Chart 8 list the calculated structural

CHART 8



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and spectroscopic (one-bond C−H coupling constants) data for the 1,3-dicarbonylic (**25**), 1,3-dithiocarbonylic (**26**), and 1,3-dimethylidenic (**27**) cyclohexane derivatives.

The structural ($\Delta r_{ax/eq}$) and spectroscopic ($\Delta^1 J_{ax/eq}$) data (Table 8 of the Supporting Information and Chart 8) provide some evidence for the additivity of $\sigma_{C-Hax} \rightarrow \pi^*_{C=Y}$ and $\pi_{C=Y} \rightarrow \sigma^*_{C-Hax}$ hyperconjugative interactions. In particular, the C−H bond length differences and one-bond C−H coupling constant differences are always larger at C(2) than at C(4,6). As discussed in section C, these differences are due mainly to changes in the length of the C(2)−H_{eq} bond length, which seems to be particularly sensitive to the hybridization change operative in the hybrid structure (C_{sp3}−H_{eq} versus C_{sp2}−H_{eq}). Of course, the C(2) methylene is adjacent to both C═Y groups, whereas C(4) and C(6) methylenes are adjacent to only one C═Y group. Nevertheless, there is undoubtedly a "saturation" of the effect since $\Delta r_{ax/eq}$ and $\Delta^1 J_{ax/eq}$ at C(2) do not reach twice the values calculated at C(4,6).

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Supporting Information Available: Calculated geometries and energies for **1**−**27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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