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$C\text{-}H_{ax}\cdots Y_{ax}$ Contacts in Cyclohexane Derivatives Revisited—Identification of Improper Hydrogen-Bonded Contacts

Antonios Kolocouris*

Faculty of Pharmacy, Department of Pharmaceutical Chemistry, University of Athens, Panepistimioupolis-Zografou, 15771 Athens, Greece

ankol@pharm.uoa.gr

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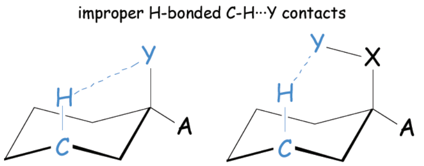

1-111

The structure of 111 cyclohexane derivatives bearing the axial substitution Y_{ax}-C was optimized at the B3LYP/6-31+G(d,p) level. The natural bond orbital analysis revealed the presence of overlap interactions between the axial substituent and the antibonding σ^*(C-Hax) orbitals; these calculated hyperconjugative interactions suggest the presence of improper H-bonded contacts. The addition of an appropriate bridging fragment between the axial substituent and cyclohexane carbon strengthens significantly the hydrogen-bonding component of the contact and several structures of axially substituted cyclohexane derivatives including such hydrogen-bonded $C\text{-}H_{ax}\cdots Y_{ax}$-C contacts were retrieved from the Cambridge Crystallographic Database. Overall, the calculations predicted that the $C\text{-}H_{ax}\cdots Y_{ax}$-C contacts in common cyclohexane derivatives that are generally thought to be steric in nature (Pauli repulsive forces) include an improper hydrogen-bonding component.

Introduction

The most important geometrical result of the strong polar hydrogen bonding X-H···Y (X, Y = N, O, F) is the elongation of the X-H bond. However, in the case of H-bonds including less polar X-H bonds a shortening of the X-H bond is mostly observed. These H-bonds, including often C-H donating groups, were characterized as improper or unconventional.[1] In both cases the H-bonded contacts are formed through an electron density transfer from the acceptor Y to the antibonding orbitals of the X-H proton donor;[2] the resonance structures, $X^{\delta-}\text{-}H^{\delta+} + :Y \leftrightarrow X^{-} + H\text{-}Y^{+}$, for a neutral H-bonded complex describe qualitatively the electron transfer. This orbital interaction and the electrostatic attraction of the X-H proton from Y explain the elongation of the X-H bond in traditional H-bonding but not the shortening in improper H-bonding.

After a period of calculations, some realistic theoretical interpretations including the combination of electrostatic and charge-transfer models have been proposed, suggesting that there is no fundamental difference between the two types of H-bonding. Whatever is the sign of X-H bond deformation, it results from a balance between elongation forces and forces pushing toward contraction. A review of the literature (the basic

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schools of thought are included in refs 3−13) revealed that the major effects causing the lengthening of the X-H bond are the attractive interaction between the positive H of X-H dipole and the electron-rich acceptor (lone pair or π electrons) and the hyperconjugative electron donation $n(\mathrm{Y}) \rightarrow \sigma^*(\mathrm{X\text{-}H})$, which are significant for electron-rich, highly polar, short X-H bonds. In the opposite side, the major X-H bond shortening contributors are the Pauli repulsive forces and the increased electrostatic attraction between the positive H and negative X (caused by a net gain of electron density at the X-H bond region in the presence of Y),[13] which are significant for less polar, electron-deficient, short X-H bonds, like C-H bonds having a negative dipole moment derivative for the isolated H-bond donor molecule.[10,13]

A successful interpretation includes the combination of a hyperconjugative interaction $n(\mathrm{Y}) \rightarrow \sigma^*(\mathrm{X\text{-}H})$ that weakens the X-H bond and a repolarization/rehybridization in which the X-H bond s-character increases, as H becomes more electropositive (Bent's rule), causing strengthening of the X-H bond. The second effect prevails, that is, an improper H bonding is observed, when the hyperconjugation is relatively weak.[12]

Experimental and theoretical studies identified the improper hydrogen-bonded contacts C(sp^3)-H$\cdots$Y (Y = O, N, S, π-donors); simple systems such as $CH_4\cdots OH_2$, $CH_4\cdots NH_3$, $CH_4\cdots FH$, $CH_4\cdots SH_2$, $CH_4\cdots Cl^-$, and $CH_4\cdots C_6H_6$ have been investigated.[14]

C(sp^3)-H$\cdots$Y contacts are formed when the axial proton of a chair cyclohexane or any cyclohexane derivative is replaced by substituent Y. These C-$H_{ax}\cdots Y_{ax}$-C contacts are generally termed in the literature as steric[15] (Pauli repulsive forces).

The recent suggestion[16] that the contacts between the axial C-H bonds and the axial tetrahedral-sulfur atom in the cyclohexane ring subunit of a 2-substituted adamantane derivative can be classified as improper hydrogen bond, despite the 1,3-diaxial orientation of the H-bonding donor and acceptor groups, motivated us to get through a prompt task: to perform ab initio calculations on simple axial cyclohexane derivatives and look for hyperconjugative overlap interactions in the C-$H_{ax}\cdots Y_{ax}$-C contacts that provide evidence for the presence of improper hydrogen-bonded contacts. Furthermore in a recent paper we commited ourselves to exploring the nature of these contacts, which are included in some relevant adamantane derivatives.[17] The structures of the model compounds **1**−**73** are shown in Scheme 1.

Results and Discussion

The geometry of the conformational ground states of molecules **1**−**73** was optimized using the B3LYP functional and the 6-31+G** basis set.[18] The natural bond orbital (NBO) analysis[2a] at the same level of theory revealed that in all molecules the C-$H_{ax}\cdots Y_{ax}$-C contacts cause an increase in % s-character and a contraction of the C-H_{ax} bonds and raise the proton positive charge of H_{ax} protons relative to the unsubstituted cyclohexane bonds (Table S1 in Supporting Information). These changes are correlated since the increase in the electropositive character of the proton causes an enhancement in the s-character and a contraction of the C-H bond according to the Bent's rule.[12] In most of the compounds **1**−**73**, the C-$H_{ax}\cdots Y_{ax}$-C contact distances were smaller than the sum of the van der Waals radii[19] of the relevant atoms, which is common in H-bonded contacts.[20]

Although these changes are usually observed in H-bonded interactions, the identification of a covalent component, i.e., the calculation of a hyperconjugative interaction $n(\mathrm{Y_{ax}}) \rightarrow \sigma^*(\mathrm{C\text{-}H_{ax}})$ or $\sigma(\mathrm{C\text{-}H})_\mathrm{Y} \rightarrow \sigma^*(\mathrm{C\text{-}H_{ax}})$ or $\sigma(\mathrm{C\text{-}H_{ax}}) \rightarrow \sigma^*(\mathrm{C\text{-}H})_\mathrm{Y}$ is really diagnostic for the presence of improper hydrogen bonding.[1c,2a]

Hyperconjugative Interactions between Substituent $\mathbf{Y_{ax}}$ and C-$\mathbf{H_{ax}}$ Bonds (Compounds 1−73). The presence of ovelap interactions in the C-$H_{ax}\cdots Y_{ax}$-C contacts of molecules **1**−**73** was examined by the NBO method, which analyzes the molecular wave function to a set of localized bond and lone pair orbitals.[2a] The hyperconjugative energies were calculated by the second-order perturbation approach[2a] and are included in Tables S1 and S2 in Supporting Information. The two main terms controlling the magnitude of hyperconjugative energy for the overlap interaction $n(\mathrm{Y}) \rightarrow \sigma^*(\mathrm{C\text{-}H})$ or $\sigma(\mathrm{C\text{-}H}) \rightarrow \sigma^*(\mathrm{C\text{-}H})$ are the difference in energy between the interacting orbitals ($\Delta\varepsilon = \varepsilon_{\sigma^*} - \varepsilon_n$ or $\varepsilon_{\sigma^*} - \varepsilon_\sigma$) in the denominator and the magnitude of the Fock matrix element F_{ij} in the nominator, which varies in parallel to the overlap matrix element, S_{ij}[21] (values of F_{ij} and $\Delta\varepsilon$ are included in Table S3 in Supporting Information). A threshold of 0.10 kcal mol^{-1} for printing second order perturbation energies was used. Selected contacts C-$H_{ax}\cdots Y_{ax}$-C bearing an improper hydrogen-bonding component are depicted in Scheme 2.

Compounds Bearing $\mathbf{Y_1}$ substituents (Scheme 1). The most significant results are described below (the detailed discussion for the hyperconjugative interactions $n(\mathrm{Y_{1,ax}}) \rightarrow \sigma^*(\mathrm{C\text{-}H_{ax}})$ can be found in Supporting Information). In compounds **2**−**8** the calculations predicted a dihydrogen-bonding[22] component in the

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(15) In a recent paper (Ribeiro, D. S.; Rittner, R. *J. Org. Chem.* **2003**, *68*, 6780) it was shown that the equatorial conformer stability relative to the axial is due to hyperconjugative overlap interactions rather than steric repulsions (or Pauli repulsions). The statement in the present work refers to the nature of C-$H_{ax}\cdots$alkyl$_{ax}$-C and C-$H_{ax}\cdots Y_{ax}$-C contacts, which is considered to be steric (Pauli repulsion).

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(18) In a study dealing with conventional hydrogen bonding (Pan, Y.; McAllister, M. A. *THEOCHEM* **1998**, *427*, 221)it was demonstrated that B3LYP/6-31+G(d,p) performed well and almost identically with other correlated methods (MP2, MP3, MP4). In the present work the compounds sample was large enough for testing of different methods and theory levels and the DFT calculations compromise accurate enough results in a reasonable time

(19) Still the most popular source of van der Waals radii is an article by Bondii, A. *J. Phys. Chem.* **1964**, *68*, 441, including the following values: H, 1.20 Å; C, 1.70 Å; O, 1.52 Å; N, 1.55 Å; F, 1.47 Å; Cl, 1.75 Å; S, 1.80 Å; P, 1.80 Å; Si, 2.10 Å. Using these values the sum of the van der Waals radii is, for example, 2.72 Å for H$\cdots$O.

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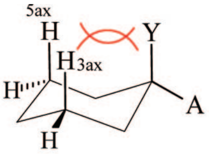
SCHEME 1. Axial Cyclohexane Derivatives with Various C-$H_{ax}\cdots Y_{ax}$-C contacts (Y = Y_1 or Y_2)



1: $Y_1 = \underline{\mathbf{H}}$ - A = H
2: $Y_1 = \underline{\mathbf{C}}H_3$ - A = H
3: $Y_1 = \underline{\mathbf{C}}H_3$ - A = *t*-Bu
4: $Y_1 = \underline{\mathbf{C}}H_2CH_3$ - A = H
5: $Y_1 = \underline{\mathbf{C}}HMe_2$ - A = H
6: $Y_1 = \underline{\mathbf{C}}HMe_2$ - A = Me
7: $Y_1 = \underline{\mathbf{C}}HMe_2$ - A = *t*-Bu
8: $Y_1 = C(\underline{\mathbf{C}}H_3)_3$ - A = H
9: $Y_1 = \underline{\mathbf{C}}H{=}CH_2$ - A = H
10: $Y_1 = \underline{\mathbf{C}}_2H$- A = H
11: $Y_1 = \underline{\mathbf{C}}_6H_5$ - A = H
12: $Y_1 = \underline{\mathbf{Si}}Me_3$ - A = H
13: $Y_1 = \underline{\mathbf{C}}N$ -A = H
14: $Y_2 = CH\underline{\mathbf{O}}$ - A = H
15: $Y_2 = C\underline{\mathbf{O}}Me$ - A = H
16: $Y_2 = C\underline{\mathbf{O}}Ph$ - A = H
17: $Y_2 = C\underline{\mathbf{O}}_2H$ - A = H
18: $Y_2 = C\underline{\mathbf{O}}_2Me$ - A = H
19: $Y_2 = C\underline{\mathbf{O}}NH_2$ - A = H
20: $Y_2 = C\underline{\mathbf{N}}HMe$ - A = H
21: $Y_2 = C\underline{\mathbf{S}}Me$ - A = H
22: $Y_1 = \underline{\mathbf{O}}H$ - A = H
23: $Y_1 = \underline{\mathbf{O}}Me$ - A = H
24: $Y_1 = \underline{\mathbf{O}}H$ - A = *t*-Bu
25: $Y_1 = \underline{\mathbf{O}}H$ - A = Ph
26: $Y_1 = \underline{\mathbf{O}}Ac$ - A = H
27: $Y_1 = \underline{\mathbf{N}}H_2$ - A = H
28: $Y_1 = \underline{\mathbf{N}}Me_2$ - A = H
29: $Y_1 = \underline{\mathbf{N}}H_2$ - A = Me
30: $Y_1 = \underline{\mathbf{N}}H_2$ - A = *t*-Bu
31: $Y_1 = \underline{\mathbf{N}}HAc$ - A = H
32: $Y_1 = \underline{\mathbf{N}}_3$ - A = H
33: $Y_1 = \underline{\mathbf{N}}O_2$ - A = H
34: $Y_2 = \underline{\mathbf{N}}H_3^+$ - A = H
35: $Y_2 = \underline{\mathbf{N}}Me_2H^+$ - A = H
36: $Y_1 = \underline{\mathbf{F}}$ - A = H
37: $Y_1 = \underline{\mathbf{F}}$ - A = *t*-Bu
38: $Y_1 = \underline{\mathbf{Cl}}$ - A = H
39: $Y_1 = \underline{\mathbf{Cl}}$ - A = *t*-Bu
40: $Y_1 = \underline{\mathbf{S}}H$ - A = H
41: $Y_1 = \underline{\mathbf{S}}Me$ - A = H
42: $Y_1 = \underline{\mathbf{S}}H$ - A = Me
43: $Y_1 = \underline{\mathbf{P}}H_2$ - A = H
44: $Y_1 = \underline{\mathbf{P}}H_2$ - A = *t*-Bu
45: Y_2, A = $C\underline{\mathbf{O}}CH_2$
46: Y_2, A = $C\underline{\mathbf{O}}(CH_2)_2$
47: Y_2, A = $C\underline{\mathbf{O}}(CH_2)_3$
48: Y_2, A = $C\underline{\mathbf{O}}(CH_2)_4$
49: Y_2, A = $C\underline{\mathbf{N}}H(CH_2)_3$
50: Y_2, A = $C\underline{\mathbf{S}}(CH_2)_3$
51: Y_2, A = $C\underline{\mathbf{O}}CH_2C_6H_4$
52: Y_2, A = $C\underline{\mathbf{O}}(CH_2)_2C_6H_4$
53: Y_2, A = $H\underline{\mathbf{O}}CH(CH_2)_3$
54: Y_2, A = $H\underline{\mathbf{O}}CH(CH_2)_4$
55: $Y_2 = CMe_2\underline{\mathbf{O}}H$ - A = H
56: $Y_2 = CMe_2\underline{\mathbf{O}}Me$ - A = H
57: $Y_2 = CMe_2\underline{\mathbf{N}}H_2$ - A = H
58: $Y_2 = CMe_2\underline{\mathbf{N}}Me_2$ - A = H
59: $Y_2 = CMe_2\underline{\mathbf{N}}Me_2H^+$ - A = H
60: $Y_2 = CMe_2\underline{\mathbf{F}}$ - A = H
61: $Y_2 = CMe_2\underline{\mathbf{Cl}}$ - A = H
62: $Y_2 = CMe_2\underline{\mathbf{SH}}$ - A = H
63: $Y_2 = CMe_2\underline{\mathbf{P}}H_2$ - A = H
64: $Y_2 = CMe_2\underline{\mathbf{C}}H{=}CH_2$ - A = H
65: $Y_2 = CMe_2\underline{\mathbf{C}}_2H$- A = H
66: $Y_2 = CMe_2\underline{\mathbf{C}}_6H_5$ - A = H
67: $Y_2 = Me_2N\text{-}\underline{\mathbf{O}}$ - A = H
68: $Y_2 = N(\underline{\mathbf{C}}H_3)_3^+$ - A = H
69: $Y_2 = P(\underline{\mathbf{C}}H_3)_3^+$ - A = H
70: $Y_2 = S\underline{\mathbf{O}}_2Me$ - A = H
71: $Y_2 = \underline{\mathbf{O}}PMe_2$ - A = H
72: $Y_2 = \underline{\mathbf{S}}PMe_2$ - A = H
73: $Y_2 = \underline{\mathbf{O}}P(OMe)_2$ - A = H

C-$H_{ax}\cdots$H-C_{alkyl} contacts (compounds **2**−**7** include dihydrogen-bonding interactions in *gauche* butane contacts); electron density from the orbital σ(C-H) of the Lewis base C-H delocalizes into the antibonding orbital σ*(C-H) of the Lewis acid C-H. The presence of attractive C-H$\cdots$H-C interactions in the alkane dimers was theoretically predicted some years ago,[23] and it has been recently proposed that the identification of a delocalization interaction σ(C-H) → σ*(C-H) assures the presence of a dihydrogen-bonded contact.[24] The C-$H_{ax}\cdots$H-C_{alkyl} contact distances in **2**−**8** are shorter that the reported distance of the highest incidence of van der Waals RCH_2-H$\cdots$H-H_2CR contacts (2.86 Å).[25] The strength of the dihydrogen-bonded component of the C-$H_{ax}\cdots$H-C contact increases progressively from a primary to a tertiary alkyl group (compounds **2**, **4**, **5**, **8**). Comparison of the second order perturbative interactions revealed that the stronger orbital interaction $\sigma(\text{C-H}_{ax}) \rightarrow \sigma^*(\text{C-H})_{alkyl}$ ($E = 0.54$ kcal mol^{-1} in **8** compared to 0.26 kcal mol^{-1} in **5** and 0.14 kcal mol^{-1} in **2**) resulted from the more effective orbital overlapping; while the energy difference between the interacting orbitals is similar in all cases ($\varepsilon_{\sigma^*(\text{C-Hax})} - \varepsilon_{\sigma(\text{C-Hax})} =$ 0.91−0.95 a.u.), the matrix elements $\langle\sigma|F|\sigma^*\rangle$ become larger on going from **2** (Y_1 = Me) to **8** (Y_1 = *t*-Bu) (0.010 a.u. in **2** vs 0.014 a.u. in **5** and 0.020 a.u. in **8**; see Table S3 in Supporting Information). Compared with the *tert*-butyl derivative **8**, the relevant contacts for the trimethylsilyl derivative **12** are characterized by longer distances and larger angles giving rise to weaker, by ∼ 0.2−0.3 kcal mol^{-1}, orbital interactions. When the alkyl group is unsaturated (Y_1 = vinyl, ethynyl, phenyl; compounds **9**−**11**) the calculations predicted similar interactions but additionally the $\pi \rightarrow \sigma^*(\text{C-H}_{ax})$ interactions in phenyl cyclohexane **11**. In the ammonium derivatives **34** and **35** a dihydrogen-bonding component was also predicted according to the $\sigma(\text{C-H}_{ax}) \rightarrow \sigma^*(\text{N-H})$ hyperconjugative interaction.

An alkyl group at the geminal cyclohexane C-1 position pushes the axial group toward C-H_{ax} bond and reduces the contact distance C-$H_{ax}\cdots Y_1$-C_{ax} resulting in enhancement of the magnitude of hyperconjugative energy. Thus, while the calculations locate the hydride donation $\sigma(\text{C3-H}_{ax}) \rightarrow \sigma^*(\text{C1}'\text{-H})_{i\text{-Pr}}$ with an interaction energy $E = 0.26$ kcal mol^{-1} for **5** (Y_1 = *i*-Pr, A = H), a stronger orbital interaction was calculated in **6** (Y_1 = *i*-Pr, A = Me) and in **7** (Y_1 = *i*-Pr, A = *t*-Bu) with $E = 0.43$ and 1.10 kcal mol^{-1} respectively (Table S1, Supporting Information).

When the acceptor group includes a second row lone-pair bearing heteroatom directly connected to cyclohexane ring (for example Y_1 = OR, NR_2) a weak interaction [$n(Y_{1,ax}) \rightarrow \sigma^*(\text{C-H}_{ax})$, $E \leq 0.4$ kcal mol^{-1}] is located because of the borderline angle values for hydrogen bonding ($\theta_{\text{C-Hax}\cdots\text{Y}}$ = 93−95°, i.e., the C-H and C−Y_1 bond vectors are nearly parallel). Hydrogen bond character decreases by decreasing the donor−acceptor angle θ(X-H$\cdots$Y) and essentially vanishes around 90°.[1b,c] The hyperconjugative interaction efficiency was increased on going

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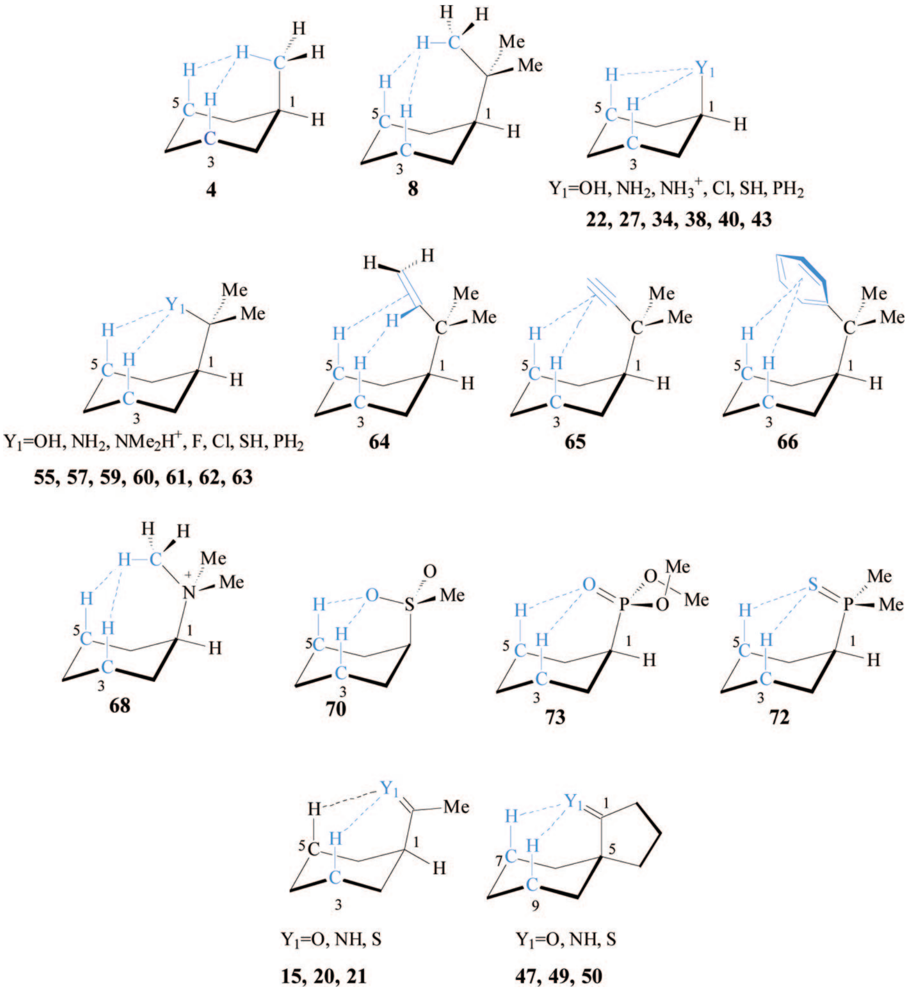
SCHEME 2. Selected Hydrogen-Bonded C-H$_{ax}\cdots$Y$_{ax}$-C Contacts (Indicated with Dotted Blue Lines) Including the Hyperconjugative Interactions $n(Y) \rightarrow \sigma^*(C\text{-}H_{ax})$ or $\sigma(C\text{-}H)_Y \rightarrow \sigma^*(C\text{-}H_{ax})$ or $\sigma^*(C\text{-}H_{ax}) \rightarrow \sigma^*(C\text{-}H)_Y$



from Y_1 = F and OH to NH_2, which is consistent with the basicity order of these groups.

When the interacting atom of the Y_1 group in C-H$_{ax}\cdots Y_1$ contacts (Scheme 1, Table S1 in Supporting Information) changes from a second row to a third row lone-pair bearing heteroatom[26] (Y_1 = PR_2, SR, Cl in compounds **38**−**44**), a substantial elongation of contact distances by 0.2−0.3 Å and an increase in contact angles by 5−7° is calculated, θ(C-H$_{ax}\cdots Y_{1,ax} \sim 100°$). The interaction energy $E[n(Y_{1,ax}) \rightarrow \sigma^*(\text{C-H}_{ax})]$ increases by 0.2−0.4 kcal mol^{-1} because of the more effective orbitals overlap ($F_{n\sigma^*}$).[27] Comparison of the NBO results for the relevant interactions $n(Y_{1,ax}) \rightarrow \sigma^*(\text{C-H}_{ax})$ revealed that the energy difference between the interacting orbitals is similar, but the matrix elements $\langle n|F|\sigma^*\rangle$ have higher values in the third row heteroatom bearing contacts (for example, $\varepsilon_{\sigma^*(\text{C-Hax})} - \varepsilon_{n(S)} = 0.69$ a.u. versus $\varepsilon_{\sigma^*(\text{C-Hax})} - \varepsilon_{n(O)} = 0.74$ a.u. and $\langle n(S)|F|\sigma^*\rangle = 0.018$ a.u. versus $\langle n(O)|F|\sigma^*\rangle = 0.010$ a.u. in compounds **40** and **22**, respectively (see Table S3 in Supporting Information).

Calculations on the complexes of hydrogen fluoride with H_2O, H_2S, $H_2C{=}O$, and $H_2C{=}S$ showed the preference of sulfur for a more "perpendicular" direction of approach to the donor atom.[28] In addition, a statistical analysis of C-H$\cdots$X-R (X = halogen) and C-H$\cdots SR_2$ contacts in crystal structures showed that their directionality disperses down to 120° compared to that of C-H$\cdots OR_2$ contacts at 180°; in their highest incidence C-H$\cdots OR_2$ contacts occur at 2.78 Å, C-H$\cdots SR_2$ at 3.21 Å, and C-H$\cdots$Cl-R at 3.17 Å.[25] Recent comparative studies of the hydrogen-bonded dimers $Me_2O\cdots HOMe$ and $Me_2S\cdots HOMe$ showed that sulfur can be an almost equally good hydrogen bond acceptor as oxygen.[29] In agreement with these observations, the calculations predicted the stronger hyperconjugative interactions for the C-H$\cdots$S contacts in compounds **40**−**42**, where the contact atom of the axial substituent is sulfur, compared to their oxygen analogs **22**, **23** (Tables S1 and S3 in Supporting Information). This result is consistent with the weak intramolecular hydrogen-bonded contacts between cyclohexane ring axial C-H donor groups and the heterocyclic sulfur atom in the 1,3-thiazolidine-5-spiro-2,2′-adamantane; the presence of

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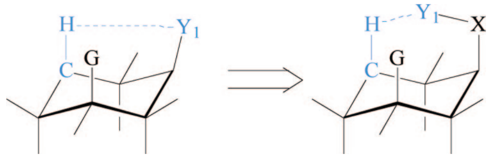
(26) For calculations of C-H$_{ax}\cdots$S contacts see, for example, refs 14d and 16 andDomagala, M.; Grabowski, S. J. *J. Phys. Chem. A* **2005**, *109*, 5683.

(27) What really determines the strength of the orbital interaction is of course the geometry of the overlapping orbitals $n(Y_{1,ax})$ and $\sigma^*(\text{C-H}_{ax})$ and not the relative orientation of the C-H and C-Y_1 bond vectors. In this work we concentrate in the second order perbutative energies $E[n(Y_{1,ax}) \rightarrow \sigma^*(\text{C-H}_{ax})]$, which reflect the result−strength of the orbitals interactions. However, when the C-H and C-Y_1 bond vectors are nearly parallel the orbital interactions are weak, whereas the addition of an appropriate fragment X_{ax} resulting in a X_{ax}-Y_1 bond vector bisecting cyclohexane ring increases the energy stabilization as will be analyzed in the next section.

(28) Platts, J. A.; Howard, S. T.; Bracke, B. R. F. *J. Am. Chem. Soc.* **1996**, *118*, 2726.

(29) Wennmohs, F.; Staemmler, V.; Schindler, M. *J. Chem. Phys.* **2003**, *119*, 3208.

SCHEME 3. General Structure of Cyclohexane Derivatives with Contacts C-$H_{ax}\cdots Y_1$-X_{ax} That Can Include Stronger H-Bonded Components than C-$H_{ax}\cdots Y_{1,ax}$ Contacts (Y_1 = H, alkyl, NR_2, OR, F, Cl, SR, PR_2, C_2H, Ph, etc)



this improper hydrogen-bonded contact C-H$\cdots$S-C was proposed using the relevant geometrical characteristics (C-H$\cdots$S-C = 2.70 Å) and some model calculations.[16] Indeed, after running NBO calculations in the optimized structure of this molecule at the B3LYP/6-31+G** level, we found two delocalizations including the tetrahedral sulfur and the C-H_{ax} bonds of the cyclohexane ring subunit of adamantane, i.e., [$n(S_{ax}) \rightarrow \sigma^*$(C-$H_{ax}$) $- E = 0.55$ and 0.80 kcal mol^{-1}].

Compounds Bearing Y_2 Substituents (Scheme 1). Orbital interactions are very weak[30] in the above intramolecular contacts as a result of the bent geometry of the C-$H_{ax}\cdots Y_{1,ax}$-C contact.[27] This fact prompted us to think for a suitable architecture that can facilitate the development of stronger overlap interactions between axial substituent and C-H_{ax} bonds.

Some obvious candidate structures are resulted through attaching an axial carbonyl functionality to the cyclohexane ring. In general, a rough design pathway includes the insertion of a carbon or heteroatom unit X between the contact atom of group $Y_{1,ax}$ and the cyclohexane carbon resulting in the axial substituent $Y_2 = X_{ax}$-Y_1 (see Scheme 3 and the relevant compounds **45−73** in Scheme 1).

In the cyclohexanes **14−21** rotation around the single C-(C=O) or C-(C=S) or C-(*C*=NH) bond favors an almost eclipsed orientation of C=O and cyclohexyl C1-C2 bonds; O=C-C1-C2 dihedral determines how much the C=O bond is pointing inside cyclohexane ring and concequently the degree of the C-H_{ax} bond shortening and of the electron transferring $n(O) \rightarrow \sigma^*$(C3-$H_{ax}$) in the C-$H_{ax}\cdots$O=$C_{ax}$-C contacts or their thiocarbonyl and imine analogs. The higher interaction energies were located for the acyl cyclohexanes **15** and **16** ($E = 0.62$ and 0.54 kcal mol^{-1}, respectively); in **15** and **16** the C=O bond vector is pointing inside to the cyclohexane ring and is rotated by 22° and 16°, respectively, from eclipsing C1-C2 bond ($\varphi_{O=C\text{-}C1\text{-}C2} = -22°, -16°$). By changing the axial substitution with Y_2 = CO-NH_2, CO-OMe, CO-OH, CO-H (compounds **19**, **18**, **17**, and **14**) the carbonyl bond points progressively outside cyclohexane ring, reducing the interaction energy and the degree of the C-H_{ax} bond shortening. Compared with the acetyl group, the imine functionality in **20** effects similar interactions. Of compounds **14−21** the strongest hyperconjugative interaction was located for thioacetyl derivative **21** ($E = 1.72$ kcal mol^{-1}, see Table S1 in Supporting Information). The replacement of the acetyl with the thioacetyl group does not change much the energy difference between the interacting orbitals ($\varepsilon_{\sigma^*(C\text{-}Hax)} - \varepsilon_{n(S)} = 0.67$ a.u. versus $\varepsilon_{\sigma^*(C\text{-}Hax)} \rightarrow\text{-}\ \varepsilon_{n(O)} = 0.73$ a.u.) but strengthens seriously the matrix elements ($F_{n\sigma^*}(S) = 0.031$ a.u. versus $F_{n\sigma^*}(O) = 0.019$ a.u.) and consequently increases the relevant hyperconjugative interaction energy $E[n(S) \rightarrow \sigma^*$(C3-$H_{ax}$)] by 1.1 kcal mol^{-1}. Thus, the better acceptor ability of the trigonal S compared to the trigonal O is predicted again in C-$H_{ax}\cdots Y_1$=C_{ax}-C contacts (see the relevant discussion for the Y_1 substituents), which agrees with the preference of sulfur for more "perpendicular" H-bonded contact geometries.[25,28]

Following these observations, we refined the structure of Scheme 3, by adding one carbon or heteroatom unit X between the substituent Y_1 and cyclohexane carbon 1-C and constraining the conformation of the resulting axial $Y_2 = X_{ax}$-Y_1 group in a way that Y_1 lone pair orbital(s) (or electron cloud in general) will be oriented above cyclohexane ring.

One such a structure can be achieved by replacing the hydrogen atoms of the axial mobile CH_2-Y_1 group by alkyl groups. In compounds **55−65** the CMe_2-Y_1 group (Y_1 = OH, OMe, NH_2, NMe_2, NMe_2H^+, SH, PH_2, F, Cl, vinyl, ethynyl) is conformationally homogeneous with the C-Y_1 bond bisecting cyclohexane ring.

The delocalization study of the B3LYP/6-31+G** optimized structures (Table S3 in Supporting Information) revealed hyperconjugative donations $n(Y_1) \rightarrow \sigma^*$(C-$H_{ax}$) with the second order energy lowering varying from 0.7 kcal mol^{-1} (in the CMe_2OH analog **55** and its O-methylated derivative **56**) and~1 kcal mol^{-1} (in the chlorine analog **61** and the CMe_2SH derivative **62**) to 1.48 and 1.58 kcal mol^{-1} in the CMe_2NH_2 and CMe_2PH_2 analogs **57** and **63**, respectively. The NBO analysis located the smaller orbital interactions for the C-$H_{ax}\cdots$F contacts in **60** [$n(F) \rightarrow \sigma^*$(C-$H_{ax}$)] $- E \approx 0.3$ kcal mol^{-1}]. An important hydride transfer [σ(C-H_{ax}) $\rightarrow \sigma^*$(N-H)] $- E = 3.09$ kcal mol^{-1}] was calculated in **59**, i.e., the protonated form of **58**, corresponding to a C-$H_{ax}\cdots$H−N^+ contact distance of 1.93 Å.

Compounds **64−66** contain unsaturated alkyl groups that have been identified in many studies to act as acceptor groups in improper H-bonded $\pi\cdots$C-H contacts.[1,14f] In the vinyl analogue **64** the double bond is oriented above C5-H_{ax} and the stabilization energy for the electron transfer $\pi \rightarrow \sigma^*$(C5-H_{ax}) was calculated to be 0.87 kcal mol^{-1}. In **65** the C-C≡C-H fragment axis coincides with cyclohexane ring bisector favoring the hyperconjugative interaction: [$\pi(C\equiv C)_{vinyl} \rightarrow \sigma^*$(C3-$H_{ax}$) $- E = 0.59$ kcal mol^{-1}]. In the lowest energy conformer of phenyl analogue **66** one methyl C-H bond is pointing above cyclohexane ring favoring dihydrogen-bonded interactions σ(C-H_{ax}) $\rightarrow \sigma^*(C\text{-}H)_{Ph}$. An interesting arrangement, which is depicted in Scheme 2, results in the next more stable conformer (being 1.43 kcal mol^{-1} above the global minimum) where the phenyl ring caps the two C-H_{ax} bonds and transfers electron charge into σ^*(C-H_{ax}) orbitals with second order energy lowering $E = 0.6−0.7$ kcal mol^{-1}.

Similarly, in molecules **67−73** a methyl group or an oxygen atom or a sulfur atom is connected with a nitrogen or a phosphorus or a sulfur atom bridge (X_{ax} = N, P, S in Scheme 3). These compounds favor a conformational ground state with the N-O, N^+-CH_3, P^+-CH_3, P-O, P-S, or S−O bond vector bisecting the cyclohexane ring, and the calculations predicted improper hydrogen-bonding components according to the hypercojugative interactions $n(Y_1) \rightarrow \sigma^*$(C-$H_{ax}$) in **67**, **70−73**, and σ(C-H) $\rightarrow \sigma^*$(C-H_{ax}) in **68** ($Y_2 = {}^+NMe_3$), and the phosphorus ylide **69** ($Y_2 = {}^+PMe_3$).

In cyclopropanone **44** the contact atoms are fairly apart (3.53 Å, Table 1), and the calculations did not locate any hyperconjugative interactions. The cyclohexanones **48** and **52** and the acyl cyclohexanes **15** and **16** have similar contact geometries, i.e., the C=O bond is eclipsing the cyclohexyl C1-C2 bond,

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[30] In order to obtain a more balanced picture when small effects are considered, in addition to the $n(Y) \rightarrow \sigma^*(\gamma$-C-$H_{ax})$ overlap interactions which are studied here, the weak hyperconjugative interactions $n(Y) \rightarrow \sigma^*(\beta$-C-H) and their significance in the geometry and energetics for six-membered heterocycles have been recently reported: Alabugin, I. V.; Manoharan, M.; Zeidan, T. A *J. Am. Chem. Soc.* **2003**, *125*, 14014.

and similar second order perturbation interaction energies. In the cyclobutanone **46** and the cyclopentanones **47** and **51** the C═O bond vector deviates by ∼ 1° and 3°, respectively, from cyclohexane ring bisector. In all cases the stabilization for the orbital interaction $n(\text{C-H}_{ax}) \rightarrow \sigma^*(\text{O})$ was not larger than 0.7 kcal mol^{-1}; the stronger interactions were located in the imine **49** and thiocarbonyl analogue **50** ($E = 1.31$ and 1.91 kcal mol^{-1}, respectively). In the cyclanols **53** and **54** unconventional H-bonded interactions O···C-H$_{ax}$ were also predicted.

The changes related to the C-H$_{ax}$ bond s-character, length, and polarization need a comment. For molecules bearing Y_1 substituents the intramolecular forces between the C-H$_{ax}$ and $Y_{1,ax}$-C groups cause in general a progressive inrease in % s-character of the hybridization state of the carbon of C-H$_{ax}$ bond, in positive charge of the axial hydrogen, and in shortening of the interacting C-H$_{ax}$ bond, relative to the unsubstituted cyclohexane bonds, by increasing the electronegative character of the contact group; the values range from −2 mÅ, 1−2 me and + 0.2% s (Y_1 = primary, secondary alkyl groups in **2−7**) to −3.8 mÅ, 19 me, +0.59% s in **27** ($Y_1 = NH_2$). The magnitude of these changes is significantly enhanced[30] for molecules in which the hydrogen-bonding acceptors $Y_1 = NR_2$, OR, F, Cl, SR, P or π-bond (vinyl, ethynyl and phenyl group) are connected through a X$_{ax}$ bridge with cyclohexane ring (contacts C-H$_{ax}$···Y═X$_{ax}$ or C-H$_{ax}$···Y-X$_{ax}$, see compounds **45−73**) resulting in stronger improper hydrogen-bonding components; this is consistent with the repolarization/rehybridization and the s-character inrease of the X-H bond, as H becomes more electropositive in hydrogen-bonded contacts X-H···Y.[12,13] Thus, for the C-H$_{ax}$···Y═X$_{ax}$ contacts the most significant changes cover the values between −4 to −6 mÅ, 22−34 me and + 1−1.1% s (see compounds **21**, **49**, **50**, **52**, and **70−72**; X$_{ax}$═Y is C$_{ax}$═O, C$_{ax}$═NH, C$_{ax}$═S, S$_{ax}$═O, P$_{ax}$═O, P$_{ax}$═S) and for the C-H$_{ax}$···Y-X$_{ax}$ contacts between −5 to −7 mÅ, 27−44 me and +1−1.5% s (see compounds **53**, **57**, and **67**; X$_{ax}$-Y is C$_{ax}$-OH, C$_{ax}$-NH$_2$, C$_{ax}$-NMe$_3$O$^-$).

Of the substituents included in **1−73**, the Me$_2$N−O$^-$ group in **67** effects the most pronounced changes (−6.8 mÅ, 44 me, + 1.53% s); the significant increase in proton positive charge of the interacting C-H$_{ax}$ groups indicates a significant electrostatic character for the C-H$_{ax}$···$^-$O-$^+$NMe$_{2,ax}$ contacts. It seems that the more pronounced changes in bond length, proton positive charge, and hybridization were affected by stronger electrostatic and improper hydrogen-bonding interactions (for further details see Supporting Information).

Analogs Retrieved from the CCDC: Hyperconjugative Interactions (compounds 74−111). The laborious searching of the Cambridge Crystallographic Database[31] using the structure of Scheme 3 was performed aiming at finding C-H$_{ax}$···Y-X$_{ax}$-C contacts bearing a significant improper hydrogen-bonding component. The appropriate retrieved structures from the CCDC were divided into four general classes **A−D** and some selected structures are shown in Scheme 4;[32] the C-H$_{ax}$···O-C$_{ax}$ contacts were found to be the most common.[1] The presence of ovelap interactions was examined by the NBO method after optimization of the structures at the B3LYP/6-31+G** level of theory. Details of the hyperconjugative interactions are discussed in Supporting Information, and the major features of these interactions are included in Table S3.

Class A: Molecules of this class include a C-X$_{ax}$(AB)-Y fragment (Schemes 3 and 4) with a tetrahedral quaternary atom X$_{ax}$ (A, B ≠ H). Thus, in compounds **74−84** the substituent Y$_{ax}$ is oriented above cyclohexane ring, favoring improper H-bonding interactions with cyclohexane ring σ*(C-H$_{ax}$) orbitals (in most of the cases the X-Y bond lies in the cyclohexane ring bisector). It is marked to note the $\pi \rightarrow \sigma^*(\text{C-H}_{ax})$ interactions in **75** and **84** and the $\sigma(\text{Si−Si}) \rightarrow \sigma^*(\text{C-H}_{ax})$ improper hydrogen-bonding interaction in the unusual structure of compound **83**.

Class B: The hits **85−87** of this class include a C-X$_{ax}$(AB)-Y fragment (Scheme 3) with a tetrahedral tertiary atom X$_{ax}$ (A ≠ H, B = H) and are analogs of the 1-hydroxyspiro[4.5]decane **53** (discussed above).

Class C: In the compounds of this family (hits **88−102**) the acceptor group Y_1 is adjusted to a favorable position for H-bonding interactions with the donor C-H$_{ax}$ bonds through a trigonal atom X$_{ax}$, which is in all cases a carbon with the exception of compound **102** having the dihydrogen-bonded contact C-H$_{ax}$···H-C−N$_{ax}$═ (Schemes 3, 4). The H-bonding acceptor is mostly a carbonyl oxygen, but some carbonyl group analogs were identified as well giving rise to the $\pi \rightarrow \sigma^*(\text{C-H}_{ax})$ orbital interaction in the allene derivative **100** ($E = 1.35$ kcal mol^{-1}) and the hyperconjugative interaction $n(\text{S}) \rightarrow \sigma^*(\text{C-H}_{ax})$ in **101** with a marked orbital overlapping ($F_{n\sigma^*} = 0.054$ a.u.) and energy lowering of 3.25 kcal mol^{-1}; the last is the strongest hyperconjugative interaction $n(\text{Y}) \rightarrow \sigma^*(\text{C-H}_{ax})$ located in this work. The ketones **92−97** or in general the α-cycloalkylacetophenone analogues are active substrates in photochemical reactions in the solid state. In these reactions the photochemical conversion of γ-hydrogen carbonyl compounds into cyclobutanols is realized through 1,4-hydroxybiradical indermediates, formed by γ-axial hydrogen abstraction from the nonbonding orbital of oxygen.[33] The results of the crystal structure−solid state reactivity/selectivity relationships study[34] showed that, of the two γ-hydrogen atoms included in the C═O···H contacts, the most proximate to carbonyl oxygen was selectively abstracted. According to the present results these ketones include improper H-bonded contacts and the calculated $n(\text{O}) \rightarrow \sigma^*(\text{C-H}_{ax})$ overlap interactions are consistent with the observed reactivity/selectivity in the photocyclization reactions.

Class D: Derivatives of the bicyclo[3.3.1]nonane **103** and its heteroanalogues **104−107**,[35] having one cyclohexane ring C-H$_{ax}$ bond (the *endo* C7-H bond) available for contact C-H$_{ax}$···Y interactions (Scheme 5), are included in this family. The compounds **108−111** were retrieved from the CCDC (Scheme 4). Of the bicyclo[3.3.1]nonane heteroanalogs, the calculations located the overlap interaction $n(\text{S}) \rightarrow \sigma^*(\text{C-H})$ in the 3-thiabicyclo[3.3.1]nonane **107** as the strongest with an energy lowering $E = 1.61$ kcal mol^{-1} (Table S3 in Supporting Information). The lowest interaction energy was calculated for the $n(\text{O}) \rightarrow \sigma^*(\text{C-H})$ hyperconjugative interaction in **104** ($E = 0.38$ kcal mol^{-1}).

It is worth mentioning that the contact distance in **110**, which is formed through the amino group protonation of the 3-methyl-3-azabicyclo[3.3.1]nonane **106**, is only 1.78 Å giving rise to the dihydrogen-bonding interaction $\sigma(\text{C7-H}_{endo}) \rightarrow \sigma^*(\text{N}^+\text{-H}_{endo})$ with a second order energy lowering $E = 4.24$ kcal mol^{-1},

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[31] Allen, F. H.; Kennard, O.; Taylor, R. *Acc. Chem. Res.* **1983**, *16*, 146.

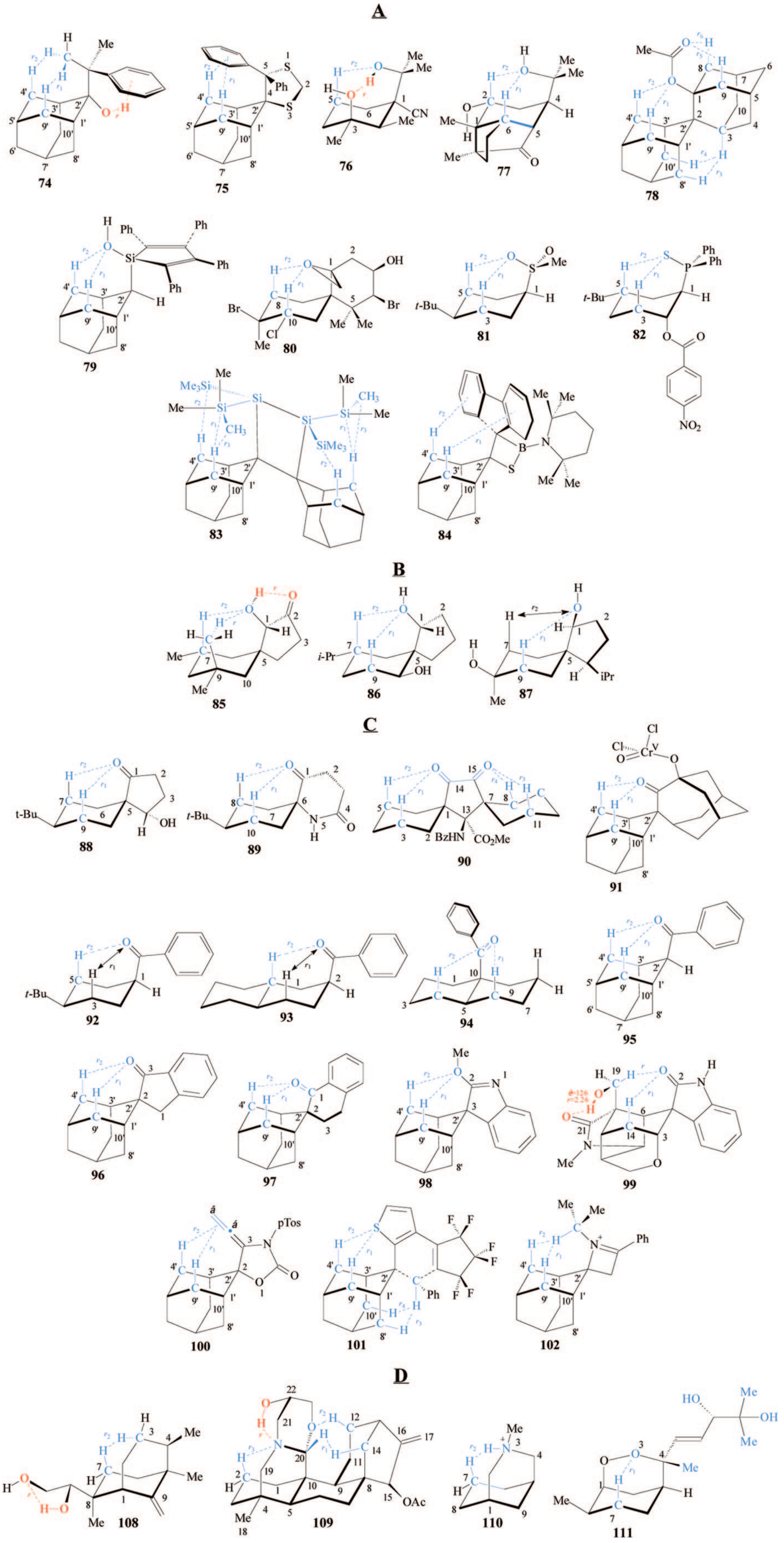
[32] The relevant references concerning molecules **74−102** and **108−111** are included in Supporting Information.

[33] Dorigo, A. E.; McCarrick, M. A.; Loncharich, R. J.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 7508.

[34] Braga, D.; Chen, S.; Filson, H.; Maini, L.; Netherton, M. R.; Patrick, B. O.; Scheffer, J. R.; Scott, C.; Xia, W. *J. Am. Chem. Soc.* **2004**, *126*, 3511.

[35] (a) Jeyaraman, R.; Avila, S. *Chem. Rev.* **1981**, *81*, 149. (b) Zefirov, N. S; Palyulin, V. A. *Top. Stereochem.* **1991**, *20*, 171.

SCHEME 4. **C-$H_{ax}\cdots Y_{ax}$-C Contacts in the Axial Cyclohexane Derivatives 74−102 and 108−111 Retrieved from the CCDC**[a]



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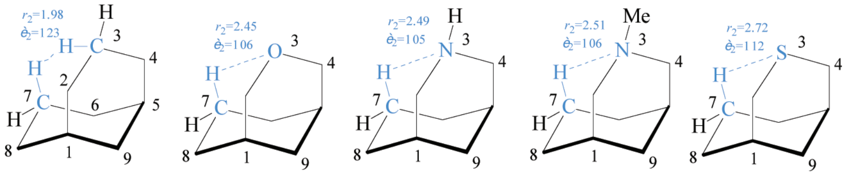
[a] Contacts including an improper H-bonded component are indicated with dotted blue lines and conventional hydrogen bonds are in red.

SCHEME 5. **C-H···Y Improper H-Bonded Contacts (Y = CH, O, N, S) in Bicyclo[3.3.1]nonanes 103−107**



103 **104** **105** **106** **107**

suggesting the presence of a significant covalent character for the C-H···H−N^+ contact.

It is clear that the replacement of the axial substituent Y_{ax} with X_{ax}-Y (see Scheme 3 and related discussion) leads to the construction of C-$H_{ax}\cdots Y{=}X_{ax}$ and C-$H_{ax}\cdots Y$-X_{ax} contacts with stronger hydrogen-bonding components, and relevant hits were retrieved from the CCDC. The highest second order perturbation energies for the interaction $n(Y) \rightarrow \sigma^*(C\text{-}H_{ax})$ in C-$H_{ax}\cdots Y{=}X_{ax}$ contacts cover values from 1.06 kcal mol^{-1} in **98** ($Y{=}X_{ax}$ is $O{=}C_{ax}$) and 1.35 kcal mol^{-1} in **100** ($Y{=}X_{ax}$ is $C_\alpha{=}C_\beta{=}C_{ax}$) to 1.91 kcal mol^{-1} in **50** ($Y{=}X_{ax}$ is $S{=}C_{ax}$) and 3.25 kcal mol^{-1} in **101** ($Y{=}X_{ax}$ is $S{=}C_{ax}$). Similarly the most effective orbital interactions in C-$H_{ax}\cdots Y$-X_{ax} contacts have energy lowering values ranging from 1.13 kcal mol^{-1} in **76** (Y-X_{ax} = HO-$CMe_{2,ax}$) and 1.48 kcal mol^{-1} in **57** (Y-X_{ax} = H_2N-$CMe_{2,ax}$) to 1.61 kcal mol^{-1} in **107** (Y-X_{ax} = S-C_{ax}) and 1.87 kcal mol^{-1} in **82** (Y-X_{ax} = S-P_{ax}). As regards contacts including a dihydrogen-bonding component, the highest second order perturbation energies range from 1.10 kcal mol^{-1} in **7** (Y-X_{ax} is H-C_{ax}), 1.85 kcal mol^{-1} in **101** (Y-X_{ax} is H-C_{ax}) and 1.24 kcal mol^{-1} in **74** (Y-X_{ax} is H-C-C_{ax}) to 3.09 kcal mol^{-1} in **59** and 4.24 kcal mol^{-1} in **110** (Y-X_{ax} is H-$^+$N-C_{ax}).

Conclusion

This paper revisits the contacts between axial substituents and axial C-H bonds in cyclohexane derivatives, which are generally thought to be steric in nature (Pauli repulsive forces). It was striking that the calculations located the small overlap interactions $n(Y_{ax}) \rightarrow \sigma^*(C\text{-}H_{ax})$, $\sigma(C\text{-}H)_Y \rightarrow \sigma^*(C\text{-}H_{ax})$, or $\sigma(C\text{-}H_{ax}) \rightarrow \sigma^*(C\text{-}H)_Y$; in addition, a common finding for all of the C-$H_{ax}\cdots Y_{ax}$-C contacts was the contraction and the increase in proton positive charge and the s-character of C-H_{ax} bonds.

It is reported here for the first time that the C-$H_{ax}\cdots Y_{ax}$-C contacts include impoper hydrogen-bonding components even in the most common axial cyclohexane derivatives. By addition of an appropriate bridging fragment between the axial substituent and cyclohexane carbon, the strength of the hydrogen-bonding component of the contact is substantially increased; structures of axially substituted cyclohexane derivatives including such hydrogen-bonded C-$H_{ax}\cdots Y_{ax}$-C contacts were retrieved from the Cambridge Crystallographic Database. Of the compounds **1−111** examined in this study the stronger orbital interactions $n(Y_{ax}) \rightarrow \sigma^*(C\text{-}H_{ax})$ were located in general for acceptor groups bearing sulfur as the contact atom.[24,26−28]

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Supporting Information Available: Details of the computational methods; detailed discussion of the overlap interactions and other descriptors (changes in bond lengths, proton positive charge, and s-character of C-H_{ax} bonds); Tables S1−S3 including selected structural parameters and hyperconjugative energies for the C-$H_{ax}\cdots Y_{ax}$-C contacts and complete second order perturbation NBO analysis for the hyperconjugative interactions; Cartesian coordinates for all the optimized compounds; references for the structures retrieved from CCDC. This material is available free of charge via the Internet at http://pubs.acs.org.

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