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Improper hydrogen-bonded cyclohexane C–$H_{ax}\cdots Y_{ax}$ contacts: experimental evidence from ^{1}H NMR spectroscopy of suitable axial cyclohexane models

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ABSTRACT

B3LYP/6-31+G(d,p) calculations predicted the presence of improper hydrogen-bonded C–$H_{ax}\cdots Y_{ax}$ contacts of different strength in cyclohexane derivatives;[1] it was predicted that the addition of an appropriate bridging fragment X_{ax} between an axial substituent Y_1 and a cyclohexane carbon would strengthen the improper hydrogen-bonded contact C–$H_{ax}\cdots Y_1$ when the X_{ax}–Y_1 bond vector bisects the cyclohexane ring. To support the theoretical predictions with experimental evidence for this effect, several 2-substituted adamantane analogues with suitable improper H-bonded C–$H_{ax}\cdots$O contacts of different strength were synthesized, as models of the corresponding cyclohexane derivatives, and their ^{1}H NMR spectra were recorded at 298 K. The ^{1}H NMR signal separation within the cyclohexane ring γ-CH_2s is increased when the B3LYP/6-31+G(d,p)-calculated strength of the H-bonded C–$H_{ax}\cdots$O=C_{ax} contact interaction is increased.

Improper H-bonded X–H···Y contacts, which often include C–H-donating groups, cause a shortening of the X–H bond in contrast to the elongation observed for strong polar hydrogen bonding (X, Y = N, O, F).[2] Whatever the sign of X–H bond deformation, it results from a balance between elongation forces and interactions toward contraction. A review of the literature revealed that the major effects causing lengthening of the X–H bond are attractive interactions between the positive H of the X–H dipole and the electron-rich acceptor group Y (lone pair or π electrons), and hyperconjugative electron donation $n(Y)\rightarrow\sigma^*(X\text{–}H)$ which are significant for electron-rich, highly polar, short X–H bonds. In contrast, the major X–H bond-shortening contributors are the Pauli repulsive forces (exchange effect) 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), which are significant for less polar, electron-deficient, short X–H bonds, such as C–H bonds having a negative dipole moment derivative for the isolated H-bond donor molecule.[3,4] Experimental and theoretical studies identified the improper hydrogen-bonded contacts C(sp^3)–H···Y (Y = O, N, S, π-donors), whilst 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 also been investigated.[5] C(sp^3)–H···Y contacts are formed when the axial proton of a cyclohexane or any cyclohexane derivative in the chair conformation is replaced by substituent Y.

In recent work[1] the contacts between axial substituent Y and axial C–H bonds in cyclohexane derivatives, which are generally termed as steric (Pauli repulsive forces), were revisited. It was striking that the calculations located the overlap interactions $n(Y_{ax})\rightarrow\sigma^*(C\text{–}H_{ax})$, that is, it was reported for the first time that the C–$H_{ax}\cdots Y_{ax}$–C contacts include an improper hydrogen-bonding component even in the most common axial cyclohexane derivatives (methyl cyclohexane, cyclohexanol, etc.).[1,6]

A significant part of that paper[1] encompassed structures with contacts in which the improper hydrogen-bonding character was enhanced because of a linker group. It was predicted that the strength of the hydrogen-bonding component or the orbital interaction $n(Y_{ax})\rightarrow\sigma^*(C\text{–}H_{ax})$[6] would be increased by the addition of an appropriate bridging fragment X between the axial substituent $Y_{1,ax}$ and the cyclohexane carbon C-1, and by constraining the conformation in such a way that the X_{ax}–Y_1 bond vector bisects the cyclohexane ring; in this arrangement the lone pair orbital(s) (or electron cloud in general) of substituent Y_1 can transfer electron charge to the $\sigma^*(C\text{–}H_{ax})$ anti-bonding orbitals (Scheme 1).[1]

The structure depicted in Scheme 1 corresponds to real systems. Axial-substituted cyclohexane derivatives having the cy-X_{ax}–Y_1 structure were retrieved from the Cambridge Crystallographic Database and the calculations revealed important improper hydrogen-bonded contacts.[1] It was therefore intriguing for us to find the

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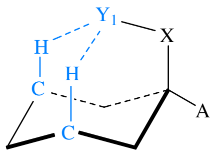


cy-X$_{ax}$-Y$_1$

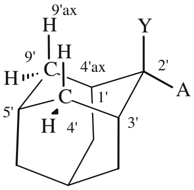
Scheme 1. Structure of cyclohexane C–H$_{ax}$···Y$_{ax}$ contacts that favor enhanced improper H-bonded interactions.

experimental evidence to support the theoretical predictions. The aim was to check, using appropriate model systems, if changes related to the proton C–H$_{ax}$ chemical shift follow changes in the strength of the improper H-bonded contact C–H$_{ax}$···Y$_{ax}$ interaction.

When an axial substituent is attached to the cyclohexane ring, a major effect of the C–H$_{ax}$···Y$_{ax}$ contact in the ^{1}H NMR spectrum is to increase the difference between the chemical shifts of the axial and equatorial protons within the γ-methylene group. In the present work, we examine whether the proton signal separation within the cyclohexane ring γ-CH$_2$ group is changed according to the different strengths of the improper H-bonded C–H$_{ax}$···Y$_{ax}$–C contacts. To observe this effect the ^{1}H NMR spectrum of the axial conformer of the desired cyclohexane derivative, being accessible only at low temperatures when ring inversion is a slow process,[7] requires analysis if the existing population of the axial conformer and spectral resolution permits. However, 2-adamantane derivatives represent models of axially substituted cyclohexanes;[8] in these molecules substituent Y is axial in the 1′-2′-3′-4′-5′-9′ adamantane cyclohexane ring (Scheme 2).

This observation motivated us to synthesize and analyze the ^{1}H NMR spectra of several 2-adamantane analogues of the relevant parent cyclohexane derivatives, which represent a subset of the structures included in Scheme 1. Thus, in this preliminary Letter the 2-adamantane analogues **1–6**[9] were prepared as models of the relevant parent cyclohexane C–H$_{ax}$···O=C contacts[10] of different improper H-bonding strength.[1] The ^{1}H NMR spectra of the adamantane derivatives **1–6** enabled a study on how the proton chemical shifts of the γ-methylene were affected by the various C–H$_{ax}$···O contacts; the proton signal separation within the cyclohexane ring γ-CH$_2$ group, Δ*δ*(γ-CH$_2$), was obtained by measuring the proton resonance separation within the 4′,9′-CH$_2$[11] in the ^{1}H NMR spectra of compounds **1–6** recorded at 298 K.

It should be noted that the study of intramolecular hydrogen-bonding contacts using NMR spectroscopy has inherent difficulties related to the definition of the reference system. Besides the simplicity in obtaining the spectra at 298 K and in the data interpretation, the models used in this work provide an additional benefit. In the unsubstituted chair cyclohexane the axial proton is located upfield with respect to the geminal equatorial proton, so the sign of the chemical shift difference between axial and equatorial protons ($\Delta\delta(\gamma\text{-CH}_2) = \delta(\gamma\text{-CH}_{ax}) - \delta(\gamma\text{-CH}_{eq})$) is negative. A C–H$_{ax}$···Y$_{ax}$–C contact will mostly shift the axial proton resonance in a downfield direction making Δ*δ*(γ-CH$_2$) smaller and more positive. In each cyclohexane ring sub-unit of the parent adamantane the protons of a CH$_2$ group are chemically equivalent, that is, the Δ*δ*(γ-CH$_2$) value is zero in the parent 'unperturbed' adamantane molecule (Scheme 2, Y = A = H). A C–H$_{ax}$···Y$_{ax}$–C contact will result in a positive value of Δ*δ*(γ-CH$_2$) which will certainly be higher in magnitude than that of the relevant cyclohexane molecules. The situation is similarly convenient for the evaluation of the changes in hybridization and bond lengths.



1: Y = C**O**Me, A = H
2: Y, A = C **O**(CH$_2$)$_2$
3: Y, A = C **O**(CH$_2$)$_3$
4: Y, A = C **O**(CH$_2$)$_4$
5: Y, A = C **O**-CH$_2$-C$_6$H$_4$
6: Y, A = C **O**-(CH$_2$)$_2$-C$_6$H$_4$

Scheme 2. Synthetic adamantane derivatives **1**–**6** (see also Scheme 3) that provide models to study cyclohexane improper H-bonded C–H$_{ax}$···Y contacts using ^{1}H NMR spectroscopy.

The geometries of the conformational ground states of molecules **1–6** were optimized using the B3LYP functional and the 6-31+G** basis set;[12] frequency calculations were also performed to confirm the minima. The natural bond orbital (NBO) analysis,[6a] which analyzes the molecular wave function to a set of localized bond and lone pair orbitals, at the same level of theory revealed that in all the molecules the C–H$_{ax}$···O contacts cause an increase in % s-character and a contraction of the C–H$_{ax}$ bonds relative to the equatorial bonds of the cyclohexane-subunit of the adamantane ring (Table 1). In compounds **1–6**, the C–H$_{ax}$···O contact distances were smaller than the sum of the van der Waals radii[13] of the relevant atoms which is always encountered in H-bonded contacts. The existence of hyperconjugative interactions $n(\text{O})\rightarrow\sigma^*(\text{C–H}_{ax})$ in molecules **1–6** was examined by the NBO method[6a] at the B3LYP/6-31+G** level of theory. The calculations located overlap interactions in all compounds **1–6**, suggesting the presence of improper hydrogen bonding in C–H$_{ax}$···Y contacts (Tables 1 and S1 in the Supplementary data). Although the first effects, that is, $r_{\text{H}\cdots\text{Y}} < r_{\text{vdw,H}} + r_{\text{vdw,Y}}$, the increase in % s-character and contraction of the C–H bond, are common in improper H-bonded contacts,[14] the identification of a covalent component in a C–H···Y contact, that is, the calculation of a hyperconjugative interaction $n(\text{Y})\rightarrow\sigma^*(\text{C–H})$ is diagnostic for the presence of improper hydrogen bonding.[6] However, the degree of hyperconjugative electron transfer is only one of the effects contributing to improper hydrogen bonding, the strength of which is reflected by the increase in the % s-character and contraction of the C–H$_{ax}$ bond length.

In the acetyl derivative **1** and the cyclohexanones **4** and **6** the C=O bond eclipses the cyclohexyl C2′–C3′ bond favoring improper H-bonding interactions with only one C–H$_{ax}$ bond compared to compounds **3** and **5** in which the C=O bond bisects the cyclohexane ring allowing oxygen lone pair(s) electrons and the π-bond of the carbonyl group to transfer electron charge to both C–H$_{ax}$ anti-bonding orbitals (Scheme 3, Tables 1 and S1). The stronger H-bonded contacts in **3** and **5** are reflected by the shorter C–H···H–C distances, the higher increase in the % s-character, and the contraction of the C–H$_{ax}$ bonds relative to the equatorial bonds (Table 1). In cyclobutanone **2** the C=O bond vector also bisects the cyclohexane ring, but the contact distances are 0.2–0.3 Å longer resulting in weaker improper H-bonded C–H$_{ax}$···O contacts with respect to the cyclopentanone **3** (Table 1). It is also interesting to analyze comparatively the magnitude of some second order perturbative interactions. For example, the stronger orbital interaction $n(\text{O})\rightarrow\sigma^*(\text{C–H}_{ax})$ in spirocyclopentanone **3** (E = 1.17 kcal mol^{-1}) compared to 0.39 and 0.58 kcal mol^{-1} in spirocyclobutanone **2** and spirocyclohexanone **4**, respectively, resulted from the more effective orbital overlapping; while the energy difference between the interacting orbitals is similar in all cases ($\varepsilon_{\sigma^*(\text{C–Hax})} - \varepsilon_{n(\text{O})} = 0.74 - 0.76$ a.u.), the matrix elements $<n|F|\sigma^*>$ are larger on going from **2** or **4** to **3** (0.016 a.u. in **2** and 0.019 a.u. in **4** vs 0.027 a.u. in **3** (see Table S1 in the Supplementary data)).

Thus, in cyclopentanones **3** and **5** the % s-character and the contraction of the C–H$_{ax}$ bonds relative to the equatorial bonds (Table 1) or the improper H-bonding interaction C–H$_{ax}$···O are

Table 1

Selected structural parameters[a,b] and hyperconjugative energies for the cyclohexane ring C–$H_{ax}\cdots$O contacts included in the adamantane derivatives 1–6 calculated at the B3LYP/6-31G+** level in addition to ^{1}H NMR chemical shifts ($CDCl_3$)[c] and signal separation of the γ-CH_2 pairs[b] of the adamantane cyclohexane ring sub-units

System	C4-H_{ax}, C9-H_{ax} C4-H_{eq}, C9–H_{eq}	$r(C4'H_{ax}\cdots Y)$ $r(C9'H_{ax}\cdots Y)$ (Å)	$\theta(C4'H_{ax}\cdots Y)$ $\theta(C9'H_{ax}\cdots Y)$ (°)	$\Delta r_{4'}$ $\Delta r_{9'}$[a] (mÅ)	Δ% s-Char.[b]	Hyperconjugative interaction (kcal mol^{-1})	$\delta_{4',9'\text{-}\mathbf{Hax}}$[d]	$\delta_{4',9'\text{-}\mathbf{Heq}}$[d]	$\Delta\delta_{4',9'}$ or $\Delta\delta(\gamma\text{-}CH_2)$[e]
1 (Y_2=COMe, A=H)[c]	1.0924, 1.0963 1.0988, 1.0985	2.40 2.77	119.0 115.0	−6.4 −2.2	1.50 0.64	$E[n_\alpha(O)\rightarrow\sigma^*(C4'-H_{ax})]$ =0.49 $\alpha = sp^{0.7}$	1.75	1.57	0.18
2 [Y_2, A =$CO(CH_2)_2$]	1.0952, 1.0963 1.0985, 1.0985	2.63 2.63	121.2 121.1	−3.3 −3.3	0.88 0.87	$E[n_\alpha(O)\rightarrow\sigma^*(C4'-H_{ax})]$=0.10 $E[n_\alpha(O)\rightarrow\sigma^*(C9'-H_{ax})]$=0.11 $E[n_\beta(O)\rightarrow\sigma^*(C4'-H_{ax})]$=0.38 $E[n_\beta(O)\rightarrow\sigma^*(C9'-H_{ax})]$=0.39 $\alpha = sp^{0.8}$, β = p $E[\pi(C{=}O\rightarrow\sigma^*(C4'-H_{ax})]$=0.13 $E[\pi(C{=}O\rightarrow\sigma^*(C9'-H_{ax})]$=0.13	2.18	1.62	0.56
3 [Y_2, A=$CO(CH_2)_3$]	1.0939, 1.0918 1.0985, 1.0988	2.33 2.46	120.7 119.2	−7.0 −4.6	1.59 1.10	$E[n_\alpha(O)\rightarrow\sigma^*(C4'-H_{ax})]$=0.20 $E[n_\alpha(O)\rightarrow\sigma^*(C9'-H_{ax})]$=0.60 $E[n_\beta(O)\rightarrow\sigma^*(C4'-H_{ax})]$=0.26 $E[n_\beta(O)\rightarrow\sigma^*(C9'-H_{ax})]$=1.17 $\alpha = sp^{0.8}$, β = p $E[\pi(C{=}O\rightarrow\sigma^*(C9'-H_{ax})]$=0.43	2.42	1.38	1.04
4 [Y_2, A=$CO(CH_2)_4$]	1.0920, 1.0983 1.0985, 1.0983	2.35 3.17	117.6 109.9	−6.5 0.0	1.46 0.18	$E[n_\alpha(O)\rightarrow\sigma^*(C4'-H_{ax})]$=0.42 $E[n_\beta(O)\rightarrow\sigma^*(C4'-H_{ax})]$=0.58 $\alpha = sp^{0.8}$, β = p $E[\pi(C{=}O\rightarrow\sigma^*(C9'-H_{ax})]$=0.37	2.01	1.57	0.44
5 [Y_2, A=CO–CH_2-C_6H_4]	1.0919, 1.0928 1.0987, 1.0985	2.32 2.38	120.7 120.2	−6.8 −5.7	1.62 1.36	$E[n_\alpha(O)\rightarrow\sigma^*(C4'-H_{ax})]$=0.37 $E[n_\alpha(O)\rightarrow\sigma^*(C9'-H_{ax})]$=0.47 $E[n_\beta(O)\rightarrow\sigma^*(C4'-H_{ax})]$=0.59 $E[n_\beta(O)\rightarrow\sigma^*(C9'-H_{ax})]$=0.98 $\alpha = sp^{0.7}$, β = p $E[\pi(C{=}O\rightarrow\sigma^*(C4'-H_{ax})]$=0.21 $E[\pi(C{=}O\rightarrow\sigma^*(C9'-H_{ax})]$=0.45	2.80	1.55	1.25
6 [Y_2, A=CO–$(CH_2)_2$-C_6H_4]	1.0905, 1.0971 1.0988, 1.0983	2.27 2.96	119.3 112.2	−8.3 −1.2	1.81 0.41	$E[n_\alpha(O)\rightarrow\sigma^*(C4'-H_{ax})]$=0.75 $E[n_\beta(O)\rightarrow\sigma^*(C9'-H_{ax})]$=1.06 $\alpha = sp^{0.8}$, β = p $E[\pi(C{=}O\rightarrow\sigma^*(C4'-H_{ax})]$ = 0.12 $E[\pi(C{=}O\rightarrow\sigma^*(C9'-H_{ax})]$ = 0.19	2.21	1.62	0.59

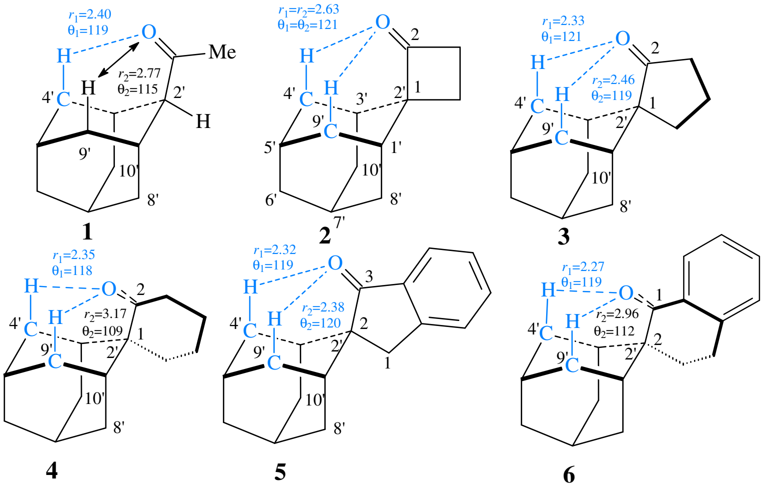
[a] $\Delta r_{4'} = r(C4'-H_{ax}) - r(C4'-H_{eq})$].

[b] Δ% s-char. = (% s-char. C4′–H_{ax} − % s-char C4′–H_{eq})].

[c] Spectra were recorded at 298 K and the signal of residual $CHCl_3$ was calibrated at 7.26 ppm.

[d] Signals for 4′,9′-H of the compounds are in general broad doublets with J_{gem} ~12 Hz.

[e] ^{1}H NMR chemical shift separation within γ-CH_2s, [$\Delta\delta(\gamma\text{-}CH_2)=\Delta\delta_{4',9'} = \delta(H_{4',9'ax}) - \delta(H_{4',9'eq})$).



Scheme 3. Improper hydrogen-bonded C–$H_{ax}\cdots O{=}C_{ax}$ contacts (colored in blue) in the axial cyclohexane models **1**–**6**.

considerably stronger than those of compounds **1**, **2**, **4**, and **6**. The stronger H-bonded contacts cause a more pronounced redistribution of electronic shielding within the cyclohexane ring γ-CH_2s effecting higher values of proton chemical shift separation within the cyclohexane ring γ-CH_2 group. Indeed, in compounds **1, 2**, **4**, and **6** the signal separation Δδ(γ-CH_2) was 0.18, 0.56, 0.44, and 0.59 ppm whereas in compounds **3** and **5** it was 1.04 and 1.25 ppm, respectively (Table 1).[15]

To summarize, in a preceding paper, the B3LYP/6-31+G(d,p) calculations predicted that the improper H-bonding character of cyclohexane $C–H_{ax}\cdots Y_1$ contacts (Scheme 1) could be increased if the $X_{ax}–Y_1$ bond vector bisects the cyclohexane ring and a sample of relevant structures was retrieved from the CCDC.[1] Experimental evidence for this structural consequence was needed and suitable $C–H_{ax}\cdots O$ contacts of different improper hydrogen-bonding interaction efficacy were prepared through the 2-substituted adamantane derivatives **1–6**, which represent the necessary cyclohexane models. The ^1H signal separation within the cyclohexane ring γ-CH_2s increases when the strength of the hydrogen-bonding interactions in the $C–H_{ax}\cdots Y_{ax}$ contacts is increased. This work presents the first example of an experimental study of improper H-bonded cyclohexane $C–H_{ax}\cdots O$ contacts.

Supplementary data

Supplementary data (computational methods used; *Table* S1 includes the complete second order perturbation NBO analysis for the hyperconjugative interactions; cartesian coordinates for the optimized conformational minima of compounds **1**–**6**; representative ^1H NMR spectra of the synthesized compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.170.

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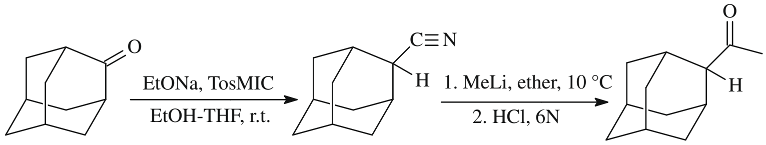

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13. Still the most popular source of van der Waals radii is an article by Bondii, A. *J. Phys. Chem.* **1964**, *68*, 441 who gives the following values H: 1.20 Å, C: 1.70 Å, O: 1.52 Å, N: 1.55 Å, F: 1.47 Å, Cl: 1.75 Å, S: 1.80 Å, P: 1.80 Å.; Si: 2.10 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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15. It is noted that changes of 0.1–1 ppm in the C–H proton chemical shift have been observed in a limited number of cases and are taken as evidence for the existence of $C–H\cdots O$ hydrogen bonds in solution. *Intermolecular*: (a) Xiang, S.; Yu, G.; Liang, Y.; Wu, L. *J. Mol. Struct.* **2006**, *789*, 43; (b) Wang, B.; Hinton, J. F.; Pulay, P. *J. Phys. Chem. A* **2003**, *107*, 4683; (c) Karger, N.; Amorim da Costa, A. M.; Ribeiro-Claro, P. J. A. *J. Phys. Chem. A* **1999**, *103*, 8672; (d) Mizuno, K.; Ochi, T.; Shindo, Y. *J. Chem. Phys.* **1998**, *109*, 9502; (e) Godfrey, P. D.; Grigsby, W. J.; Nichols, P. J.; Raston, C. L. *J. Am. Chem. Soc.* **1997**, *119*, 9283; *Intramolecular*: (f) Donati, A.; Ristori, S.; Bonechi, C.; Panza, L.; Nartini, G.; Rossi, C. *J. Am. Chem. Soc.* **2002**, *124*, 8778; (g) Barone, V.; Bolognese, A.; Correale, G.; Diurno, M. V.; Monterrey-Gomez, I.; Mazzoni, O. *J. Mol. Graph. Model.* **2001**, *19*, 318; (h) Nagawa, Y.; Yamagaki, T.; Nakanishi, H.; Nakagawa, M.; Tezuka, T. *Tetrahedron Lett.* **1998**, *39*, 1393.