Stereochemical dependence of NMR *geminal* spin–spin coupling constants

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In this work it was sought to explore the versatility of *geminal* spin–spin coupling constants, $^2J_{XY}$ SSCCs, as probes for stereochemical studies. A set of compounds, where their experimental $^2J_{XY}$ SSCCs through the X–C–Y molecular fragment are predicted to be sensitive to hyperconjugative interactions involving either bonding or antibonding orbitals containing the C carbon atom ('coupling pathway'), were analyzed. SSCC calculations were performed for some selected examples using the second order polarization propagator approximation (SOPPA) method or within the DFT-B3LYP framework. Hyperconjugative interactions were calculated within the Natural Bond Orbital (NBO) approach. Results are condensed in two qualitative rules: Rule I_M – hyperconjugative interactions transferring charge into the coupling pathway yield a positive increase to the Fermi contact (FC), contribution to $^2K_{XY}$ reduced spin–spin coupling constants (RSSCC), and Rule II_M – hyperconjugative interactions transferring charge from the coupling pathway yield a negative increase to the FC contribution to $^2K_{XY}$ RSSCC. Copyright © 2008 John Wiley & Sons, Ltd.

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Introduction

At present, *vicinal* spin–spin coupling constants (SSCCs) continue to be the most commonly used NMR parameter for stereochemical analyses.[1–3] Moreover, during the last decade there has been a notable increase in the systematic use of one- and two-bond SSCCs for studying conformations and configurations.[4–11] Following this trend, this work describes a substantial increase in ^2J SSCCs potential as probes to analyze stereochemical aspects in organic compounds. In order to avoid any misinterpretation, when the magnetogyric ratio of both coupling nuclei are of unlike signs the respective reduced spin–spin coupling, K (RSSCC), Eqn (1) will also be quoted.

$$K_{AB} = 4\pi^2 \frac{J_{AB}}{h \, \gamma_A \gamma_B} \tag{1}$$

In all cases cited above, the SSCC stereochemical behavior is mainly determined by the Fermi contact (FC) term. At present it is known that the transmission of that term through the molecular electronic structure is like that of the Fermi Hole.[12–14] This means that electron delocalization interactions should be adequate 'carriers' for transmitting the FC term corresponding to long-range SSCCs. For one- and two-bond SSCCs this pictorial representation is not adequate, but according to previous papers,[15–18] hyperconjugative interactions should affect their FC terms notably. For instance, for a $^2K_{XY}$ RSSCC through the X–C–Y molecular fragment, where C is a carbon atom, in some compounds the following two rules were verified to hold: (I) Hyperconjugative interactions transferring charge into any of the σ^*_{X-C} or σ^*_{C-Y} antibonding orbitals belonging to the X–C–Y fragment yield a positive increase to $^2K_{XY}$. (II) Hyperconjugative interactions transferring charge from any of the σ_{X-C} or σ_{C-Y} bonding orbitals, yield a negative increase to $^2K_{XY}$.

Rules like I and II increase notably the scope of NMR spectroscopy to perform stereochemical analyses using *geminal* SSCCs,

since they are on the basis of the behavior of stereoelectronic interactions whose trends are well known within the Organic Chemistry community. However, they are not enough to describe some experimental trends, which are particularly notorious when one of the coupling nuclei corresponds to a lone-pair bearing atom. For this reason, this work was sought to extend those rules to cover a larger number of *geminal* couplings than that covered by afore mentioned rules. There are many examples of $^2J_{XY}$ SSCCs through the X–C–Y fragment that are sensitive to hyperconjugative interactions involving either bonding or antibonding orbitals containing C, but neither X nor Y atoms. This sensitivity suggests that in those cases such bonding and antibonding orbitals should also be considered part of the $^2J_{XY}$ SSCC 'coupling pathway'. This means that all four σ_{C-Za}, σ_{C-Zb}, σ_{C-X} and σ_{C-Y} bonding, as well as all the corresponding antibonding orbitals should be considered as the $^2J_{XY}$ SSCC coupling pathway (Fig. 1). Accordingly, the most obvious way of generalizing Rules I and II is to change them, respectively, to:
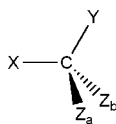
Rule I_M: Interactions transferring charge into any of the antibonding orbitals belonging to the coupling pathway yield a positive increase to $^2K_{XY}$ RSSCC.

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Figure 1. The $^2J_{XY}$ SSCC coupling pathway; it includes all four bonding and four antibonding orbitals corresponding to the four bonds shown in this diagram.

(1) X = Cl, Br and I
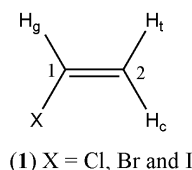
Scheme 1. Haloethene derivaties where experimental $^2J_{C1,Hc}$ and $2J_{C1,Ht}$ SSCCs show unusually large differences.

Rule II$_M$: Interactions transferring charge from any of the bonding orbitals belonging to the coupling pathway yield a negative increase to $^2K_{XY}$ RSSCC, i.e. an algebraic decrease.

The coupling pathway is as shown in Fig. 1 when C is a sp^3 hybridized C atom, but when C hybridization is sp^2, one of σ_{C-Za} and σ_{C-Zb} bonding orbitals corresponds to an orbital of π-symmetry. Similar considerations hold for the respective antibonding orbitals.

Results and Discussion

1-X-ethenes (X=Cl, Br, I)

Several unusual $^2J_{CH}$ SSCCs in haloethenes (Scheme 1) were reported by Marshall[19] and, on intuitive grounds, it can be expected that they are very sensitive to hyperconjugative interactions involving the equivalent of either the σ_{C-Z} bonding or its antibonding orbital σ^*_{C-Z} (Fig. 1). Marshall observed that in 1-haloethene compounds the *geminal* $^2J_{CH}$ coupling involving the proton *cis* to the halogen atom is notably more negative than the coupling to a proton either *geminal* or *trans* to the halogen atom. Three examples are discussed here for 1-X-ethenes, **1**, where X=Cl, Br and I. Calculated and experimental $^2J_{C1Hc}$ and $^2J_{C1Ht}$ SSCCs are compared in Table 1. In these compounds the $\sigma_{C1=C2}$ and $\pi_{C1=C2}$ bonding and $\sigma^*_{C1=C2}$ and $\pi^*_{C1=C2}$ antibonding orbitals belong to both coupling pathways, which simplifies notably a qualitative analysis of hyperconjugative effects on such *geminal* couplings.

Calculated SSCCs displayed in Table 1 include all four isotropic terms, i.e. FC, spin-dipolar (SD), paramagnetic spin-orbit (PSO)

Table 1. Comparison between calculated and experimental $^2J_{C1Ht}$ and $^2J_{C1Hc}$ (in Hz) for compounds **1** (X=Cl, Br, I)

	$^2J_{C1Ht}$		$^2J_{C1Hc}$	
X	Exp.[a]	Theor.	Exp.[a]	Theor.
Cl	+7.1	+8.7	−8.3	−7.6
Br	+7.5	+8.3	−8.5	−7.3
I	+4.15	+5.9	−7.8	−6.4

[a] Taken from Ref. [19].

Table 2. Main hyperconjugative interactions (in kcal mol^{-1}) playing an important role when applying Rules I$_M$ and II$_M$ to $^2J_{CH}$ SSCC values displayed in Table 1[a]

	Interactions	X = Cl	X = Br	X = I
1	LP$_1$(X)→$\sigma^*_{C1=C2}$	1.7	1.8	1.8
2	LP$_2$(X)→$\sigma^*_{C1=C2}$	5.2	4.7	4.0
3	LP$_3$(X)→$\pi^*_{C1=C2}$	17.1	14.2	11.4
4	σ_{C2-Ht}→σ^*_{C1-X}	8.9	9.4	9.2
5	σ_{C2-Hc}→σ^*_{C1-Hg}	5.1	5.2	5.2
6	σ_{C1-Hg}→σ^*_{C2-Hc}	4.2	4.4	4.8

[a] LP$_1$, LP$_2$ and LP$_3$ stand for lone pairs of atom X with the lowest; the second lowest and the highest energy, respectively.

and diamagnetic spin-orbit (DSO). The presence of heavy halogen atoms in these compounds would suggest that relativistic effects could be important. However, it would be out of the qualitative scope of this work to consider them since the nonrelativistic approach used reproduce correctly the experimental trend. Besides, such trends are by far originated in the FC term. For $^2J_{C1Hc}$ the σ_{C2-Ht} orbital plays the role of σ_{C-Z} while for $^2J_{C1Ht}$ that role is played by the σ_{C2-Hc} orbital (Fig. 1). To verify if Rule I$_M$ predicts qualitatively the SSCC trend displayed in Table 1, NBO hyperconjugative interactions above the 0.5 kcal mol^{-1} in **1** (X=Cl, Br, I) involving the $\sigma^*_{C1=C2}$, $\pi^*_{C1=C2}$, σ^*_{C2-Hc} and σ^*_{C2-Ht} antibonding orbitals are shown in Table 2. According to Rule I$_M$ interactions 1, 2 and 3 yield an increase to both $^2J_{C1Hc}$ and $^2J_{C1Ht}$ SSCCs.

The sum of these two interactions show a monotonic trend along the Cl, Br, I series; this trend is compatible with that of $^2J_{C1Ht}$ along the same series (Table 1). The strong interaction 4 is expected to yield a strong negative contribution to $^2J_{C1Hc}$ SSCC, Rule II$_M$, while interactions 5 and 6 are mutually the back-donation of each other and therefore they are expected to yield opposite effects on the $^2J_{C1Hc}$ SSCC. Since their difference is less than 1 kcal mol^{-1} they can be neglected when performing a qualitative analysis of the $^2J_{C1Hc}$ SSCC trend. Therefore, the experimental trend shown in Table 1 seems to originate mainly in interaction 4, supporting the qualitative validity of Rule I$_M$.

One of the coupling nuclei corresponds to a lone-pair bearing atom

When one of the coupling nuclei in $^2J_{XY}$ bears a lone pair the studied effects are notably enhanced because of the strong hyperconjugative interactions (anomeric effect) involving that nonbonding electron pair; it is highlighted that no back-donation to this hyperconjugative interaction can take place. A case in point is $^2K_{NHsyn}$ and $^2K_{NHanti}$ RSSCCs in **2a** and **2b**, Fig. 2, where the role of the σ^*_{C-Z} antibonding orbital, Fig. 1, is played in the former by the $\sigma^*_{C-Hanti}$ while in the latter by the σ^*_{C-Hsyn} antibonding orbitals. The $\sigma^*_{C-Hanti}$ is involved in a strong LP(N)→$\sigma^*_{C-Hanti}$ interaction, which according to Rule I$_M$ yields an increase to the $^2K_{NHsyn}$ RSSCC.[18,19] According to the former version of Rule I$_M$[17] this interaction yields also an increase to $^2K_{NHanti}$, although this effect seems to be notably smaller than the former. This suggests that, in compounds like **2a**, interactions that transfer charge into antibonding orbitals (σ^*_{C-Z} in Fig. 1) are notably more efficient for increasing $^2K_{XY}$ than those transferring charge into the σ^*_{C-X} and σ^*_{C-Y} antibonding orbitals.

Since σ_{C-Hsyn} and σ_{N-OH} bonds are antiperiplanar to each other and the antibonding orbital of the latter is a very good electron acceptor, the corresponding interaction yields a negative contribution to $^2K_{N-Hsyn}$, suggesting that the efficiency quoted in the last sentence is unexpectedly large. Comparing $^2K_{NHsyn}$ in **2a** with similar RSSCC in **2b** indicates that σ^*_{C-CMe}, in the latter plays the role of $\sigma^*_{C-Hanti}$ in **2a**. Since σ^*_{C-CMe} is a better electron acceptor than $\sigma^*_{C-Hanti}$, it is expected that $^2K_{NHanti}$ in **2b** would be larger than that in **2a,** in agreement with the experimental trend shown in Fig. 2.

Methyl formate (**3**) and *N*-methylformamide (**4**) (Fig. 3) are taken as model compounds to study with greater detail the lone-pair orientation effect on *geminal* couplings involving one lone-pair bearing atom. The following convention is adopted in both compounds for any oxygen atom, i.e. the lone-pair lowest in energy is labeled $LP_1(O)$, while that highest in energy is labeled $LP_2(O)$.

In **3**, the experimental SSCCs $^2J^{17}_{O_{Me}H_f} = 38$ Hz[22] and $^2J^{17}_{O_cH_f} = 10.5$ Hz,[23] are known. Not many experimental values
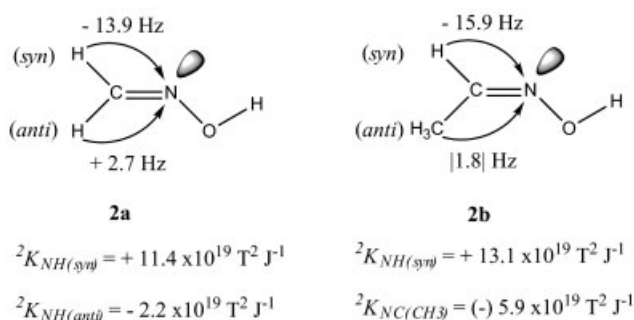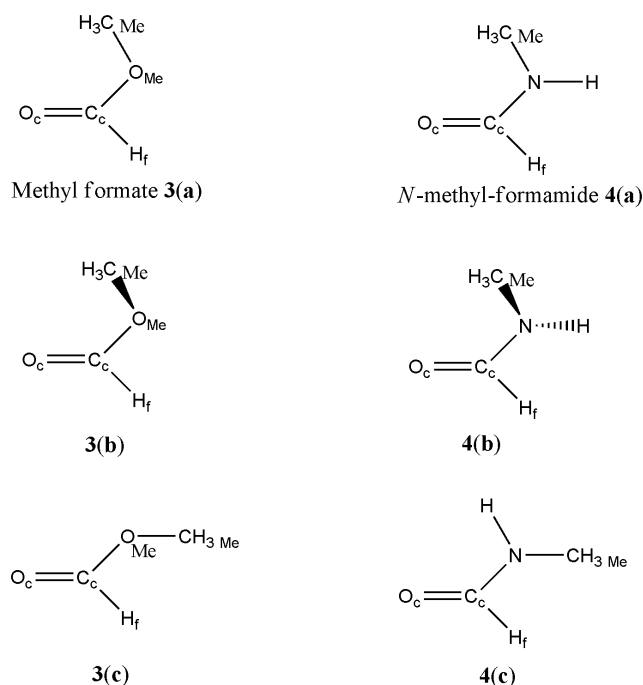
for *geminal* couplings involving ^{17}O are known. The hybridization of the O_{Me} atom is sp^2 because of the strong conjugative effect between the O_{Me} lone-pair of pure π character, $LP_2(O_{Me})$, and the carbonyl π-electronic system. The s-*cis* conformation (Fig. 3) is preferred[22] and the in-plane O_{Me} lone-pair, $LP_1(O_{Me})$, is *syn* to the formyl $\sigma_{C_c-H_f}$ bond, i.e. this is a configuration similar to that of $^2J_{NHsyn} = -13.9$ Hz in **2a**. In compound **3**, $^2J^{17}_{O_{Me}H_f}$ is transmitted also through the C_c atom, which is known[24] to be a very efficient coupling pathway owing to the very strong $LP_2(O_c) \rightarrow \sigma^*_{C_c-O_{Me}}$ and $LP_2(O_c) \rightarrow \sigma^*_{C_c-H_f}$, interactions.[17] Therefore, the FC term of $^2J^{17}_{O_{Me}H_f}$ in **3** is transmitted through two different coupling pathways; one of them is analogous to that of $^2J^{15}_{NH_f}$, in *N*-methyl formamide (**4**) transmitted through the C_c atom ($^{15}N\gamma < 0$ and $^{17}O\gamma < 0$). In compound **4**, the N lone pair, like the $LP_2(O_{Me})$ in **3**, is of pure π-character. Assuming additivity of contributions to $^2J^{17}_{O_{Me}H_f}$ transmitted through both coupling pathways, each of them can be estimated by calculating the respective *geminal* SSCCs for conformers **a**, **b** and **c** of compounds **3** and **4**. For both compounds **a** is the most stable conformer, while conformations **b** and **c** are obtained through 90° and 180° rotations around the C_c-O_{Me} and C_c-N bonds, respectively (Fig. 3).

Calculations were carried out within both the coupled perturbed density functional theory (CP-DFT)[25–27] and the SOPPA[28–30] methods, and the results are displayed in Table 3, where SOPPA results are in better agreement with experimental values, although both calculations follow well the experimental trends. The $^2J^{17}_{O_cH_f}$ SSCC in compound **3** involves the H_f proton, which is *syn*-periplanar to one lobe of the in-plane carbonyl O lone-pair of pure p character, $LP_2(O_c)$. To the authors' knowledge, this coupling, in compound **4**, is experimentally unknown. As it is shown in Table 3, the respective RSSCCs for **3b** and **4b** are close to each other, indicating that their coupling pathways are of similar efficiency, and that the $^2K_{O_{Me}H_f}$ coupling pathway originating in the $LP_1(O_{Me})$ orientation is almost inhibited for conformation **3b**. The $^2K_{NH_f}$ in **4**[31] is practically the same for conformations (**4a, b, c**) suggesting that in **3b**, the $^2K_{O_{Me}H_f}$ RSSCC is only transmitted through the C_c atom. Therefore,

Figure 2. Examples of $^2J_{NH}$ SSCCs notably affected by hyperconjugative interactions involving the equivalent to either σ_{C-Z} or σ^*_{C-Z} (Fig. 1) (taken from Refs. [20,21]). Since $^{15}N\gamma < 0$ the respective RSSCCs are also shown.

Figure 3. Conformations for compounds **3** and **4** considered in this work.

Table 3. SOPPA and DFT calculations of total (FC + SD + PSO + DSO) $^2J^{17}_{O_{Me}H_f}$ and $^2J^{17}_{O_cH_f}$ in **3a, b, c** and $^2J_{NH_f}$ and $^2J^{17}_{O_cH_f}$ in **4a, b, c** SSCCs and their respective FC contribution (in Hz). For SOPPA calculations also the total RSSCCs values are also shown (in 10^{19} T^2 J^{-1})

		3[a]			4[b]		
Method		a	b	c	a	b	c
SOPPA	$^2J_{XH_f}$	−39.0	−24.3	−13.2	−17.7	−17.5	−17.7
	FC	−39.7	−25.0	−14.1	−18.1	−17.8	−18.1
	$^2K_{XH_f}$	23.9	14.9	8.1	14.5	14.4	14.5
DFT	$^2J_{XH_f}$	−45.1	−26.8	−14.3	−20.4	−19.1	−20.4
	FC	−46.1	−27.7	−15.5	−20.9	−19.5	−20.9
SOPPA	$^2J_{O_cH_f}{}^c$	−8.7	−9.6	−8.0	−6.8	−11.1	−6.8
	FC	−9.7	−10.8	−9.1	−8.2	−12.7	−8.2
	$^2K_{O_cH_f}$	5.3	5.9	4.9	4.2	6.8	4.2
DFT	$^2J_{O_cH_f}$	−9.5	−10.7	−8.8	−7.2	−12.5	−7.4
	FC	−10.6	−12.0	−10.0	−8.8	−14.2	−8.9

[a] X = $^{17}O_{Me}$ for compound **3** and its experimental value is 38 Hz;[22]
[b] X = ^{15}N for compound **4**, and the experimental values, measured in DMSO, for **a** and **c** conformations are − 15.67 Hz, and − 13.63 Hz, respectively.[31]
[c] In **3** experimental $^2J_{O_cH_f} = ca$ 10.5 Hz;[23] in **4** it is unknown.

Table 4. The NBO hyperconjugative interactions (kcal mol^{-1}) for conformers **3a** and **3c**, which are expected to affect $^2J^{17}{}_{O_{Me}H_f}$ RSSCC values, are displayed

	Interaction	3a	3c
1	$LP_2(O_{Me}) \rightarrow \pi^*{}_{C_c=O_c}$	51.0	46.7
2	$LP_1(O_{Me}) \rightarrow \sigma^*{}_{C_c=O_c}$	7.8	1.8
3	$LP_2(O_c) \rightarrow \sigma^*{}_{C_c-O_{Me}}$	32.9	34.0
4	$LP_2(O_c) \rightarrow \sigma^*{}_{C_c-H_f}$	21.6	23.2
5	$LP_1(O_{Me}) \rightarrow \sigma^*{}_{C_c-H_f}$	1.7	4.5
6	$\sigma_{CMe-O_{Me}} \rightarrow \sigma^*{}_{C_c-H_f}$	1.9	<0.5
7	$\sigma_{CMe-O_{Me}} \rightarrow \sigma^*{}_{C_c=O_c}$	<0.5	3.3
8	$\sigma_{C_c=O_c} \rightarrow \sigma^*{}_{CMe-O_{Me}}$	<0.5	1.9
9	$\sigma_{C_c-H_f} \rightarrow \sigma^*{}_{CMe-O_{Me}}$	5.5	1.5

the difference of $^2K_{O_{Me}H_f}$ between **3a** and **3b** can be ascribed to the contribution of $^2K_{O_{Me}H_f}$, transmitted through the $LP_1(O_{Me})$ orientation effect, i.e. 9×10^{19} T^2 J^{-1}.

In **3a** for $^2K^{17}{}_{O_cH_f}$ $\sigma_{C_c-O_{Me}}$ plays the role of σ_{C-Z} bond (Fig. 1), while in **4a** for $2K_{NH_f}$ this is done by σ_{C_c-N}; $\sigma^*{}_{C_c-O_{Me}}$ is a better electron acceptor than $\sigma^*{}_{C_c-N}$. Therefore, the calculated trend of $^2K^{17}{}_{O_cH_f}$ is compatible with the predictions made when applying Rule I$_M$.

In Table 4 are collected several NBO hyperconjugative interactions for 3a, c, which affect the $^2K^{17}{}_{O_{Me}H_f}$ RSSCC, according to Rules I$_M$ and II$_M$. For both conformations the carbonyl $\pi_{C_c=O_c}$ and $\sigma_{C_c=O_c}$ bonds are playing the role of σ_{C-Za} and σ_{C-Zb} bonds (Fig. 1).

As discussed above, the $^2K^{17}{}_{O_{Me}H_f}$ RSSCC is expected to be very sensitive to charge transfer interactions involving either σ_{C-Za} and σ_{C-Zb} bonds or any of their antibonding orbitals, like interactions (1) and (2) in Table 4. These two interactions are notably stronger for **3a** than for **3c** and the lone-pair orientation effect in **3** seems to originate mainly in these two interactions. It is noted that interactions 5, 6 and 7, according to Rule I$_M$, correspond to positive contributions to the $^2K^{17}{}_{O_{Me}H_f}$ RSSCC, while interactions 8 and 9 correspond to negative contributions (Rule

II$_M$). Interactions 3 and 4 depend on the OMe group conformation, being somewhat weaker for **a** than for **c**. In the former, there is a close proximity between the O_c atom and methyl protons, and a slight inhibition of the $LP_2(O_c) \rightarrow \sigma^*{}_{C_c-O_{Me}}$ and $LP_2(O_c) \rightarrow \sigma^*{}_{C_c-H_f}$ negative hyperconjugative interactions[32] takes place, suggesting that weak hydrogen bonds of the type O_c-H-C_{Me}[33] are operating. The strong interactions 3 and 4 are typical of a carbonyl group and they form part of the 'through C_c coupling pathway'.[17]

A critical discussion

Results presented above for **1**, **2** and **3** are compatible with Rules I$_M$ and II$_M$. However, as shown in previous papers, it was observed that in some compounds hyperconjugative interactions involving only σ_{X-C} or σ_{C-Y} bonding and $\sigma^*{}_{X-C}$ or $\sigma^*{}_{C-Y}$ antibonding orbitals (Fig. 1) are enough to describe some $^2J_{XY}$ experimental trends. Seeking to shed light on molecular features that define such different behaviors, $^2J_{C2,Hexo}$ and $^2J_{C2,Hendo}$ in norbornanone, **5**, 2-*exo*-norbornanol, **6**, and $^2J_{C1,Heq}$ and $^2J_{C1,Hax}$ in the *axial*, **7**, and *equatorial*, **8**, isomers *cis* and *trans* of 4-*t*-butyl-cyclohexanol, and $^2J_{CH}$ SSCCs in ethyl crotonate, **9** were measured and their respective signs, whenever possible, were also determined experimentally (Fig. 4).

In Table 5 for compounds **5**, **6**, **7** and **8** experimental SSCCs are compared with their DFT-calculated values, while in Table 6 for compounds **5** and **6** are displayed hyperconjugative interactions that are expected, according to Rules I and II, to affect the FC term of SSCCs displayed in the Table 5. The following notation is employed in Table 6, D and A stands for 'donor bonding orbital' and 'acceptor antibonding orbital', respectively; HI stands for hyperconjugative interaction, Back for 'back donation' and *diff* stands for the HI – Back difference (in kcal mol^{-1}).

Although no linear correlation can be expected to hold between SSCCs displayed in Table 5 and hyperconjugative interactions displayed in Table 6, each *diff* value is taken to be approximately indicative of the whole effect of both a hyperconjugative interaction and its back-donation in the respective FC term. Similar criterion is applied to the sum of the respective differences. Positive (negative) *diff* values correspond to negative (positive)
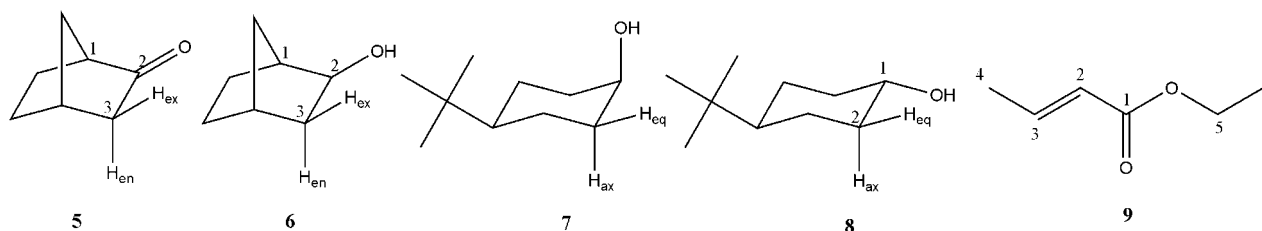
Figure 4. Molecular structures for: norbornanone (**5**), 2-*exo*-norbornanol (**6**), cis-4-*t*-butylcyclohexanol (**7**), trans-4-*t*-butylcyclohexanol (**8**) and ethyl crotonate (**9**).

Table 5. For compounds **5**, **6**, **7**, and **8** calculated and experimental $^2J_{CH}$ SSCCs (in Hz) studied in this work are compared. Calculated values include the four isotropic terms of SSCCs

	5		6			7		8	
SSCC	Exp	Theo	Exp	Theo	SSCC	Exp	Theo	Exp	Theo
$^2J_{C2-Hendo}$	3.9	−3.5	+2.6	1.4	$^2J_{C1-Heq}$	−5.9	−4.5	−5.9	−4.4
$^2J_{C2-Hexo}$	6.8	−6.4	−5.9	−5.6	$^2J_{C1-Hax}$	<1	0.8	−6.1	−5.2

The sign for compound 5 was not possible to determine using HSQC-TOCSY-IPAP but for 6–8 the signs were determined.

Table 6. Main hyperconjugative interactions expected to affect, according to Rules I and II, $^2J_{C2,Hendo}$ and $^2J_{C2,Hexo}$ SSCCs (in Hz) in norbornanone, **5**, and in 2-*exo*-norbornanol, **6**. (HI values are in kcal mol^{-1})

5: FC term of $^2J_{C2,Hendo} = -3.6$ Hz					6: FC term of $^2J_{C2,Hendo} = +1.5$ Hz				
D	A	HI	Back	*diff*	D	A	HI	Back	*diff*
LP$_1$(O)	σ^*_{C2-C3}	24.6	–	–	LP$_1$(O)	σ^*_{C2-C3}	6.4	–	–
σ_{C3-Hen}	σ^*_{C1-C2}	1.6	0.7	0.9	σ_{C3-Hen}	σ^*_{C1-C2}	0.7	0.7	0.0
σ_{C3-Hen}	σ^*_{C4-C7}	2.0	2.8	−0.8	σ_{C3-Hen}	σ^*_{C4-C7}	2.2	2.6	−0.4
σ_{C3-Hen}	σ^*_{C2-O}	3.5	–	3.5	σ_{C3-Hen}	σ^*_{C2-O}	1.2	–	1.2
					σ_{C3-Hen}	σ_{C3-C7}	–	2.9	−2.9
		Sum of *diff*		3.6			Sum of *diff*		−2.1

5: FC term of $^2J_{C2,Hexo} = -6.6$ Hz					6: FC term of $^2J_{C2,Hexo} = -6$ Hz				
D	A	HI	Back	*diff*	D	A	HI	Back	*diff*
LP$_1$(O)	σ^*_{C2-C3}	24.6	–	–	LP$_1$(O)	σ^*_{C2-C3}	6.4	–	–
σ_{C3-Hex}	σ^*_{C1-C2}	1.0	–	1.0	σ_{C3-Hex}	σ^*_{C1-C2}	0.7	0.6	0.1
σ_{C3-Hex}	σ^*_{C4-C5}	2.9	2.0	0.9	σ_{C3-Hex}	σ^*_{C4-C5}	2.9	1.9	1.0
σ_{C3-Hex}	$\pi^*_{C2=O}$	5.6	1.2	4.4	σ_{C3-Hex}	σ^*_{C2-Hn}	0.7	0.6	0.1
					σ_{C3-Hex}	σ^*_{C2-O}	1.9	–	1.9
		Sum of *diff*		6.3			Sum of *diff*		3.1

Table 7. Main hyperconjugative interactions affecting $^2J_{C1,Heq}$ and $^2J_{C1,Hax}$ SSCCs in *cis*-4-*t*-butylcyclohexanol (**7**)

7a. FC term of $^2J_{C1,Hax} = 0.7$ Hz					7b. FC term of $^2J_{C1,Heq} = -4.5$ Hz				
D	A	HI	Back	*diff*	D	A	HI	Back	*diff*
LP$_{1,2}$(O)	σ^*_{C1-C2}	7.0	–	–	LP$_{1,2}$(O)	σ^*_{C1-C2}	7.0	–	–
σ_{C2-Hax}	σ^*_{C1-O}	5.2	1.4	3.8	σ_{C2-Heq}	σ^*_{C1-C6}	3.5	2.3	1.2
σ_{C2-Hax}	σ^*_{C3-Hax}	3.2	3.5	−0.3	σ_{C2-Heq}	σ^*_{C3-ax}	0.6	–	0.6
σ_{C2-C3}	σ^*_{C1-H}	2.0	3.8	−1.8	σ_{C2-Heq}	σ^*_{C3-C4}	3.7	1.8	1.9
σ_{C2-Heq}	σ^*_{C3-C4}	3.7	1.8	1.9	σ_{C2-Hax}	σ^*_{C1-O}	5.2	1.4	3.8
σ_{C2-Heq}	σ^*_{C1-C6}	3.5	2.3	1.2	σ_{C2-C3}	σ^*_{C1-H}	2.0	3.8	−1.8
LP$_2$(O)	σ^*_{C2-Hax}	–	0.7	−0.7					
		Sum of *diff*		4.1			Sum of *diff*		5.7

contributions to the respective SSCC. On the other hand, in **5** and **6** the LP$_1$(O)$\rightarrow\sigma^*_{C2-C3}$ interaction yields a positive increase for both $^2J_{C2,Hendo}$ and $^2J_{C2,Hexo}$ SSCCs, although in **5** this contribution is notably larger than in **6**. Taking into account these considerations it is observed that, either comparing analogous couplings in both compounds, or different couplings in the same compound, values displayed in Table 6 are compatible, within a reasonable degree, with the unmodified rules I and II commented in the Introduction.

Similar data for **7** are displayed in Table 7 for $^2J_{C1,Heq}$ and $^2J_{C1,Hax}$, and for **8** are displayed in Table 8. In Table 7 for both cases (7a and 7b), the second and third interactions correspond to those quoted in rules I and II, and in the next three rows are displayed interactions playing an important role in Rules I$_M$ and II$_M$. Taking into account those three rows, the value of $^2J_{C1,Heq}$ SSCC, Table 7a, is compatible with Rules I$_M$ and II$_M$. But, this is not the case for $^2J_{C1,Hax}$ SSCC, Table 7a, where neither Rules I and II nor I$_M$ and II$_M$ can provide a rationalization of that SSCC. It is observed that an unusual *vicinal* hyperconjugative interaction of type LP$_2$(O)$\rightarrow\sigma^*_{C2-Hax} = 0.7$ kcal/mol is calculated and, at least at first sight, it is suggested that $^2J_{C1,Hax}$ SSCC in **7** cannot be rationalized within the Rules I$_M$ and II$_M$ owing to such unusual interaction. On the other hand, data displayed in Table 8 show that the $^2J_{C1,Hax}$

and $^2J_{C1,Heq}$ trend is compatible with both Rules I and II and Rules I$_M$ and II$_M$, although the latter works better.

Main differences between hyperconjugative interactions displayed in Tables 7 and 8 suggest that hyperconjugative interactions involving σ_{C-Za} or σ_{C-Zb} and their respective antibonding orbitals (Fig. 1, Rules I$_M$ and II$_M$), play an important role in the $^2J_{XY}$ coupling pathway whenever there is a significant difference between a hyperconjugative and its back-donation interactions. A couple of examples are, the $\sigma_{C2-Hax}\rightarrow\sigma^*_{C1-O} = 5.2$ kcal mol^{-1} hyperconjugative interaction and it back-donation, 1.4 kcal mol^{-1}; and $\sigma_{C2-Heq}\rightarrow\sigma^*_{C3-C4} = 3.7$ kcal mol^{-1} and its back-donation, 1.8 kcal mol^{-1}; according to Rule II$_M$, they should correspond to a decrease of $^2J_{C1,Hax}$, concomitantly producing a positive increase in the column headed *diff* for the respective $^2J_{C1,Heq}$ SSCC. This observation is in line with results reported in Fig. 2, where interactions involving a lone-pair define the observed trend, and no back-donation is known for a lone-pair.

Ethyl crotonate, **9,** was taken as another model compound to measure their *geminal* J_{CH} SSCCs including their signs. In Table 9 such experimental couplings are compared with the corresponding calculated values at the B3LYP/EPR-III level. All four isotropic contributions are included. In general, the agreement

Table 8. Main hyperconjugative interactions affecting $^2J_{C1,Heq}$ and $^2J_{C1,Hax}$ SSCCs in *trans*-4-*t*-butyl-cyclohexanol (**8**)

	8: FC term of $^2J_{C1,Hax} = -5.3$					8: FC term of $^2J_{C1,Heq} = -4.3$ Hz			
D	A	HI	Back	*diff*	D	A	HI	Back	*diff*
$LP_{1,2}(O)$	σ^*_{C1-C2}	7.4	–	–	$LP_{1,2}(O)$	σ^*_{C1-C2}	7.4	–	–
σ_{C2-Hax}	σ^*_{C1-Hax}	0.6	–	0.6	σ_{C2-Heq}	σ^*_{C3-Hax}	3.5	2.3	1.2
σ_{C2-Hax}	σ^*_{C3-Hax}	3.3	3.3	0.0	σ_{C2-Heq}	σ^*_{C3-C4}	3.7	1.8	1.9
σ_{C2-C3}	σ^*_{C1-O}	2.7	2.0	0.7	σ_{C2-C3}	σ^*_{C1-O}	2.7	2.0	0.7
σ_{C2-Heq}	σ^*_{C3-Hax}	3.5	2.3	1.2	σ_{C2-Hax}	σ^*_{C1-Hax}	0.6	–	0.6
σ_{C2-Heq}	σ^*_{C3-C4}	3.7	1.8	1.9					
σ_{C2-Hax}	σ^*_{C3-C4}	3.3	3.5	−0.2					
		Sum of *diff*	4.2				Sum of *diff*	4.4	

Table 9. Experimental and calculated SSCCs in compound **9** are compared (in Hz). Bonding[a] and antibonding occupancies are given in 10^{-3} units

SSCC	$J_{exp.}$	$J_{calc.}$	A $\sigma_{X-C} + \sigma^b_{C-Y}$	B $\sigma^*_{X-C} + \sigma^*_{C-Y}$	C $\sigma_{C-Za} + \sigma_{C-Zb}$	D $\sigma^*_{C-Za} + \sigma^*_{C-Zb}$
$^2J_{C_5H_6}$	−4.8	−2.9	−7−9	4 + 4	−9−9	4 + 4
$^2J_{C_6H_5}$	−2.5	−1.2	−7−10	8 + 18	−10-10	26 + 18
$^2J_{C_1H_2}$	3.6[c]	+3.0	−23−21	65 + 17	−14−101	12 + 55
$^2J_{C_2H_3}$	−1.8	−1.6	−14−25	12 + 18	−12	8
$^2J_{C_3H_2}$	−0.5	+0.4	−21−25	17 + 18	−23	65
$^2J_{C_3H_4}$	−7.4	−6.3	−12−20	8 + 8	−12−20	8 + 8
$^2J_{C_4H_3}$	+3.7	+5.6	−25−12	18 + 8	−14−101	12 + 55

[a] Bonding occupancies were obtained by subtracting 2.000 from each of them.
[b] See Fig. 1.
[c] This sign could not be determined experimentally.

between experimental and calculated values is very good. However, there is a discrepancy between the theoretical and experimental sign for $^2J_{C_3H_2}$ whose four isotropic terms are, respectively, FC = +2.1, SD = +0.0, PSO = −1.3 and DSO = −0.4 Hz. The main contributions are the FC and PSO terms, their signs being unlike; apparently, this discrepancy could originate in an overestimation of the FC term. It is interesting to note that total hyperconjugative interactions from one bonding orbital can be described as a whole by its NBO occupancy. A similar assertion holds for total hyperconjugative interactions into a given antibonding orbital and its NBO occupancy. Therefore, in the same Table 9, for each SSCC are shown the occupancies of relevant (see Fig. 1) bonding and antibonding orbitals.

When analyzing data presented in Table 9 it is important to recall the following two points: (i) Rules I_M and II_M are only qualitative; actually when the perturbation theory is applied, hyperconjugative interactions affect mainly the respective orbital energy gaps. (ii) For similar reasons, it is expected that hyperconjugative interactions and *geminal* SSCCs are not linearly related; two different SSCCs could be affected differently by two hyperconjugative interactions of the same intensity.

When comparing two different SSCCs it is necessary to identify how bonding and antibonding orbitals in compound **9** are playing the different roles shown in Fig. 1. For instance, in $^2J_{C_4H_3}$ SSCCs, the two bonds under heading **A** (Table 9) are the $\sigma_{C_4-C_H}$ and $\sigma_{C_3-C_4}$ bonds, for heading **B** the antibonding orbitals correspond to the bonds quoted in **A**; for **C**, two $\sigma_{C_4-C_H}$ bonds, and for **D**, the corresponding antibonding orbitals of the bonds quoted in **C**. The **A** and **C** headings, according to Rule II_M, correspond to negative increases to the corresponding J, while those under **B** and **D** headings, according to Rule I_M correspond to positive increases. For instance, the comparison between $^2J_{C_4H_3}$ and $^2J_{C_3H_4}$ SSCCs shows that the former has positive contributions coming mainly from the $\sigma^*_{C_2=C_3}$ and $\pi^*_{C_2=C_3}$ antibonding orbitals. The comparison between $^2J_{C_6H_5}$ and $^2J_{C_5H_6}$ SSCCs shows that the latter has positive contributions coming from both $\sigma^*_{C_5-H}$ and $\sigma^*_{C_5-O}$ antibonding orbitals. When comparing $^2J_{C_4H_3}$ and $^2J_{C_5H_6}$ SSCCs it is observed that in the former there are negative contributions coming from interactions of type $\sigma_{C_4-H_4} \rightarrow \pi^*_{C_2=H_3}$, which are not present in the latter. It is also interesting to compare $^2J_{C_4H_3} = 3.7$ Hz with the similar one, $^2J_{C_{Me6},H_4} = +4.4$ Hz in *trans*-2-methyl-penta-1,3-diene.[17] Since the carbonyl π-electronic system is expected to be a better electron acceptor than the C=C π-system, the occupancy of the $\pi^*_{C=C}$ is expected to be larger than that of $\pi^*_{C_2=C_3}$ in **9**, in line with the corresponding experimental couplings.

Concluding Remarks

The close relationship between the transmission of the Fermi hole and the FC term of SSCCs[12–14] suggests that hyperconjugative interactions play an important role for transmitting that contribution to SSCCs. In fact, for long-range SSCCs ^nJ, n > 3, even in saturated compounds,[32,34] σ-hyperconjugative interactions define their coupling pathways (except for SSCCs dominated by a 'through-space mechanism'[35]). For shorter range, i.e. n ≤ 3, the FC term is notably affected by hyperconjugative interactions.[15,16]

The important advantage of relating efficient coupling pathways with stereospecific delocalization interactions is fully appreciated

when intending to use SSCCs as probes to perform stereochemical studies since hyperconjugative interactions follow very well known trends in organic compounds. For this reason were presented several experimental SSCCs where their trends suggest that hyperconjugative interactions involving either the C–Z bonds or their antibonding orbitals (Fig. 1), affect notably the geminal $^2J_{XY}$ SSCCs. Such examples suggest a generalization of rules that are known[17] to be valid in limited types of compounds. These generalizations are, Rule I_M: interactions transferring charge into any of the antibonding orbitals belonging to the coupling pathway yield a positive increase to the FC contribution to $^2K_{XY}$ RSSCC; Rule II_M: interactions transferring charge from any of the bonding orbitals belonging to the coupling pathway yield a negative increase to the FC contribution to $^2K_{XY}$ RSSCC, where the $^2K_{XY}$ coupling pathway is defined by the four bonding and antibonding orbitals displayed in Fig. 1. These observations raise the following question: why experimental trends of geminal SSCCs in several compounds can be described with Rules I and II while in other compounds their trends can only be described using Rules I_M and II_M? Apparently, the answer is this; when the strength of hyperconjugative interactions involving either the σ_{C-Za} or σ_{C-Zb} bonding orbitals differs from that of their respective back-donations, the latter rules become important.

When applying any of the rules quoted above it is important to keep in mind that they refer only to qualitative trends. Therefore, it cannot be expected that there is any general linear relationship connecting the magnitude of hyperconjugative interactions and the FC contribution to geminal SSCCs; this is particularly true when considering coupling pathways with different hybridized atoms. This assertion is easy to understand if it is recalled that the theoretical calculation of SSCCs is a difficult task for Quantum Chemistry.[36] However, if it is thought that perturbation theory is applied using both occupied and vacant localized molecular orbitals, then from a qualitative point of view they can be considered to behave like NBO core, bonding, lone pairs, Rydberg and antibonding orbitals. Then, hyperconjugative interactions affect mainly the relevant energy gap in each virtual transition. Obviously, nobody can claim that in this way a precise description of SSCCs can be achieved.

It is also important to stress that exceptions to the rules presented in this work cannot be ruled out, being likely that several exceptions could be found. However, it is quite stimulating to observe that in a very recent paper[37] Krivdin et al. predicted a very strong stereochemical dependence of $^2J_{SeC}$ SSCC in divinylselenide. In fact, they reported $^2J_{SeC}$ ca 0 Hz for s-trans and $^2J_{SeC}$ ca 60 Hz for s-cis conformations. For the latter, it is expected that strong hyperconjugative interactions between the Se lone pairs and the antibonding orbitals of the vinylic double bond take place. Such result is compatible with Rule I_M.

Computational Details

Geometry optimizations for compounds **1**, **3–9** were performed with the Gaussian 03 package of programs[38] at the MP2[39]/aug-cc-pVTZ level of approximation. For iodine derivative the Sadlej pVTZ[40] basis set was used for optimization and for SSCC calculations while for chlorine and bromine the cc-pVTZ basis set was applied.

In **3** and **4** SSCC calculations were performed with the 2.0 version of the Dalton program package[41] at the SOPPA,[28–30] and at DFT-B3LYP[42–46] levels, where cc-pVTZ-J basis set was used

for all atoms. The cc-pVTZ-J basis set is obtained from the aug-cc-pVTZ-J one[47] by removing the most diffuse s- and p-functions for H and the most diffuse s-, p- and d-functions for C, N and O.

Calculations of all four terms for SSCCs in mono-haloethene derivatives (Table 1), of $^2J_{XY}$ SSCCs were carried out using CP-DFT method with B3LYP functional, which corresponds to the Lee et al.'s correlated functional and the exchange part is treated according to the Becke's three parameters approach. The EPR-III basis set[48] was employed, which is of a triple-zeta quality and includes diffuse and polarization functions. It is important to recall that coupling constants calculated at the B3LYP/EPR-III level are close to the basis-set converged values.[49] The NBO 5.0 program was implemented into Gaussian 03 and applied to perform hyperconjugative interactions analyses.[50]

Experimental

The compounds **5**, **6** and **9** are commercially available and were used without further purification, the NMR data for compounds **7** and **8** were obtained from the literature.[51] The NMR experiments for compounds (**5**), (**6**) and (**9**) were performed at 300 K using solutions of 20 mg of solute in 0.6 ml of CDCl$_3$ on a Bruker Avance III 300 spectrometer equipped with an inverse 5 mm probe with z-gradient, operating at 300 and 75 MHz for ^{1}H and ^{13}C, respectively. The $^2J_{CH}$ couplings values and sign were measured using the HSQC-TOCSY-IPAP pulse sequence.[52] The HSQC-TOCSY-IPAP experiments were performed with 16 scans for each of the 512 F1 increments, 16 384 data points in F2, AQ 0.0142 s, mixing time (MT) 20 ms, SW 3188.7 Hz and 2D SW 18 027.7 Hz.

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