

# The effect of carbonyl group in the asymmetry of ${}^3,4J_{\text{CH}}$ coupling constants in norbornanones

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A rationalization of the known difference between the  ${}^3,4J_{\text{C}_4\text{H}_1}$  and  ${}^3,4J_{\text{C}_1\text{H}_4}$  couplings transmitted mainly through the 7-bridge in norbornanone is presented in terms of the effects of hyperconjugative interactions involving the carbonyl group. Theoretical and experimental studies of  ${}^3,4J_{\text{CH}}$  couplings were carried out in 3-*endo*- and 3-*exo*-X-2-norbornanone derivatives (X = Cl, Br) and in *exo*- and *endo*-2-norbornone compounds. Hyperconjugative interactions were studied with the natural bond orbital (NBO) method. Hyperconjugative interactions involving the carbonyl  $\pi^*_{\text{C}_2=\text{O}}$  and  $\sigma^*_{\text{C}_2=\text{O}}$  antibonding orbitals produce a decrease of three-bond contribution to both  ${}^3,4J_{\text{C}_4\text{H}_1}$  and  ${}^3,4J_{\text{C}_1\text{H}_4}$  couplings. However, the latter antibonding orbital also undergoes a strong  $\sigma_{\text{C}_3-\text{C}_4} \rightarrow \sigma^*_{\text{C}_2=\text{O}}$  interaction, which defines an additional coupling pathway for  ${}^3,4J_{\text{C}_4\text{H}_1}$  but not for  ${}^3,4J_{\text{C}_1\text{H}_4}$ . This pathway is similar to that known for homoallylic couplings, the only difference being the nature of the intermediate antibonding orbital; i.e. for  ${}^3,4J_{\text{C}_4\text{H}_1}$  it is of  $\sigma^*$ -type, while in homoallylic couplings it is of  $\pi^*$ -type. Copyright © 2007 John Wiley & Sons, Ltd.

**Keywords:** NMR;  ${}^3,4J_{\text{CH}}$ ; carbonyl group; norbornanones

## Introduction

Since the early work by Karplus,<sup>[1–3]</sup> the vicinal  ${}^3J_{\text{HH}}$  indirect spin–spin coupling constant is extensively used as an important probe to determine the structure, stereochemistry and conformation in organic and bioorganic molecules. Many experimental and theoretical works have been published in which several effects affecting the original Karplus relationship have been discussed:<sup>[4]</sup> for instance, substituent effects,<sup>[5,6]</sup> substituent orientation,<sup>[7]</sup> bond angles along the coupling pathway,<sup>[8,9]</sup> the presence of a heteroatom along the coupling pathway<sup>[10,11]</sup> and hyperconjugative interactions involving bonding or antibonding orbitals belonging to the coupling pathway.<sup>[12,13]</sup> Karplus-like relationships describing dihedral angle dependence of  ${}^3J_{\text{CH}}$  coupling have also been established.<sup>[14–16]</sup> Both types of coupling constant,  ${}^3J_{\text{HH}}$  and  ${}^3J_{\text{CH}}$ , seem to be similarly affected by factors such as those quoted above.<sup>[17–19]</sup> Aydin and Günther, on the basis of the data obtained from some deuterated norbornane and adamantane derivatives, proposed an expression for their dihedral angle dependence.<sup>[20,21]</sup>

It should be recalled that in norbornane and norbornanone derivatives the through-the-bridge formal  ${}^3J_{\text{CH}}$  couplings are actually  ${}^3,4J_{\text{CH}}$  couplings,<sup>[13]</sup> where there are two four-bond coupling pathways. In several instances, the four-bond contributions are negligibly small; however, in the present case, for reasons shown below, they are taken into account and therefore such couplings are labeled as  ${}^3,4J_{\text{CH}}$ .

Parella *et al.*<sup>[22]</sup> have reported the experimental  ${}^3,4J_{\text{CH}}$  obtained for norbornanone (**1**) and 2-substituted norbornanes (**6**) and (**7**) (Scheme 1). They observed in norbornanone (**1**)  ${}^3,4J_{\text{C}_1\text{H}_4} = 5.2$  Hz and  ${}^3,4J_{\text{C}_4\text{H}_1} = 8.9$  Hz. However, no explicit rationalization was provided by the authors why  ${}^3,4J_{\text{C}_1\text{H}_4}$  and  ${}^3,4J_{\text{C}_4\text{H}_1}$  are so different in norbornanone.

In this short communication, the large difference between  ${}^3,4J_{\text{C}_1\text{H}_4}$  and  ${}^3,4J_{\text{C}_4\text{H}_1}$  couplings reported by Parella *et al.*<sup>[22]</sup> in norbornanone is investigated looking for an adequate rationalization

that could provide a deeper insight into the role played by the carbonyl group in defining such a notorious asymmetry between these two couplings. To this end, the seven compounds displayed in Scheme 1 were studied from both experimental and theoretical approaches.

## Results and Discussion

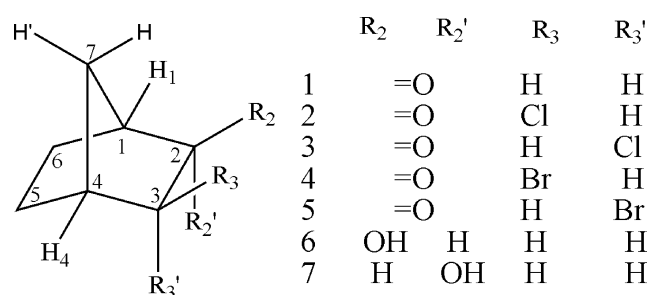
${}^3,4J_{\text{CH}}$  couplings were measured using the HSQC-TOCSY-IPAP pulse sequence<sup>[23]</sup> on a Bruker Avancell<sup>+</sup> 300 spectrometer equipped with an inverse 5 mm probe with z-gradient, operating at 300 and 75 MHz for  ${}^1\text{H}$  and  ${}^{13}\text{C}$ , respectively. Samples were prepared as solutions of 20 mg of solute in 0.6 ml of  $\text{CDCl}_3$ . Spectra were taken at 300 K.  ${}^3J_{\text{CH}}$  couplings in compounds **1** to **7** were also calculated using the CP-DFT methodology<sup>[24]</sup> as implemented in the Gaussian03 package of programs.<sup>[25]</sup> Knowing the important role played by hyperconjugative interactions in the Fermi contact transmission in long-range couplings, hyperconjugative interactions were evaluated using the natural bond orbital (NBO)<sup>[26]</sup> method as implemented in the Gaussian03 program. The B3LYP hybrid functional was used in all calculations, which consists of the hybrid Becke+Hartree-Fock exchange and the Lee–Yang–Parr

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**Scheme 1.** Studied compounds: norbornanone (**1**), 3-substituted norbornanones (**2–5**) and norborneol (**6** and **7**).

**Table 1.** Comparison between theoretical and experimental  ${}^3J_{\text{CH}}$  coupling constant (Hz) for compounds **1–7**

	${}^3J_{\text{C}_1\text{H}_4}$			${}^3J_{\text{C}_4\text{H}_1}$		
	FC	Total	Experimental	FC	Total	Experimental
( <b>1</b> )	+4.9	+4.9	+5.2	+9.3	+9.3	+8.5
( <b>2</b> )	+5.0	+5.0	+5.3	+8.6	+8.6	+8.4
( <b>3</b> )	+4.9	+4.9	+5.0	+8.4	+8.4	+8.0
( <b>4</b> )	+5.0	+5.0	+5.3	+8.8	+8.8	+8.6
( <b>5</b> )	+4.8	+4.8	+4.9	+8.4	+8.4	+8.1
( <b>6</b> )	+8.3	+8.3	+8.4	+9.7	+9.7	+9.5
( <b>7</b> )	+7.2	+7.2	+7.7	+9.3	+9.3	+8.8

correlation functional.<sup>[27–29]</sup> For geometry optimizations, the aug-cc-pVTZ basis set<sup>[30]</sup> was chosen. Calculations of all four terms of  ${}^3J_{\text{CH}}$  [Fermi contact (FC); spin dipolar (SD); paramagnetic spin orbit (PSO); and diamagnetic spin orbit (DSO)] were carried out using the EPR-III basis set,<sup>[31]</sup> which is of a triple-zeta quality and includes diffuse and polarization functions. The *s* part of this basis set is enhanced to better reproduce the electronic density in the nuclear regions, since this point is particularly important when calculating the FC term.

An excellent agreement between the calculated and experimental  ${}^3J_{\text{CH}}$  couplings was observed for compounds (**1–7**) (Table 1). For all these couplings, the SD term is around 0 Hz, while the PSO and DSO terms cancel each other. It is observed that  ${}^3J_{\text{C}_1\text{H}_4}$  couplings are around 5.0 Hz for all norbornanone compounds (**1–5**), which is very small for a  $\text{C}_1\text{–C}_7\text{–C}_4\text{–H}_4$  coupling pathway with a dihedral angle quite close to  $180^\circ$ , while for the same compounds the  ${}^3J_{\text{C}_4\text{H}_1}$  couplings are *ca* 8.5 Hz, which are similar to those reported by Aydin and Günther,<sup>[20]</sup> with respective dihedral angle

( $\text{C}_4\text{–C}_7\text{–C}_1\text{–H}_1$ ) close to  $178^\circ$  (Table 2). In order to assess the role played by the carbonyl group in defining the difference between  ${}^3J_{\text{C}_1\text{H}_4}$  and  ${}^3J_{\text{C}_4\text{H}_1}$  in norbornanone derivatives, similar couplings were measured in *exo*-2-norborneol (**6**) and *endo*-2-norborneol (**7**) (Table 1). It is noteworthy that the asymmetry in these two couplings, although notably reduced in comparison with those in compound **1**, is also present in the two norborneol derivatives. From a comparison of the couplings displayed in Table 1, it can be concluded that the difference between  ${}^3J_{\text{C}_1\text{H}_4}$  and  ${}^3J_{\text{C}_4\text{H}_1}$  couplings in **1** originates mainly in a reduction of  ${}^3J_{\text{C}_1\text{H}_4}$ , probably due to the influence of the carbonyl group, and not due to an increase in the  ${}^3J_{\text{C}_4\text{H}_1}$  coupling.

Any hyperconjugative interaction taking charge from a  ${}^3J_{\text{CH}}$  coupling pathway leads to a reduction in the corresponding  ${}^3J_{\text{CH}}$  coupling.<sup>[12,13]</sup> Two hyperconjugative interactions,  $\sigma_{\text{C}_1\text{–C}_7} \rightarrow \pi^*\text{C}_2=\text{O}$  and  $\sigma_{\text{C}_1\text{–C}_7} \rightarrow \sigma^*\text{C}_2=\text{O}$  (Table 2), are noteworthy in norbornanones and they are expected to yield a reduction in both the three-bond contribution to  ${}^3J_{\text{C}_1\text{H}_4}$  and  ${}^3J_{\text{C}_4\text{H}_1}$  couplings. Although the  $\sigma_{\text{C}_1\text{–C}_7}$  bond plays a different role in the three-bond coupling pathway of  ${}^3J_{\text{C}_1\text{H}_4}$  and  ${}^3J_{\text{C}_4\text{H}_1}$ , this difference is not considered here since the present analysis is only qualitative. Nevertheless, it should be noted the strong  $\sigma_{\text{C}_3\text{–C}_4} \rightarrow \sigma^*\text{C}_2=\text{O}$  hyperconjugative interaction involves the  $\sigma_{\text{C}_3\text{–C}_4}$  bond orbital which contains the  $\text{C}_4$  coupling nucleus of the  ${}^3J_{\text{C}_4\text{H}_1}$  coupling. It should also be noted that in norbornanones (**1–5**) the  $\sigma_{\text{C}_3\text{–C}_4} \rightarrow \sigma^*\text{C}_2=\text{O}$  interaction is stronger than the  $\sigma_{\text{C}_1\text{–C}_7} \rightarrow \sigma^*\text{C}_2=\text{O}$  interaction (Table 2). These two last interactions,  $\sigma_{\text{C}_1\text{–C}_7} \rightarrow \sigma^*\text{C}_2=\text{O}$  and  $\sigma_{\text{C}_3\text{–C}_4} \rightarrow \sigma^*\text{C}_2=\text{O}$ , define an additional coupling pathway for  ${}^3J_{\text{C}_4\text{H}_1}$  but not for  ${}^3J_{\text{C}_1\text{H}_4}$ , providing an adequate rationalization to explain the observed difference between the  ${}^3J_{\text{C}_1\text{H}_4}$  and  ${}^3J_{\text{C}_4\text{H}_1}$  couplings in norbornanone derivatives. It can be observed that the additional coupling pathway for  ${}^3J_{\text{C}_4\text{H}_1}$  is quite similar to that observed<sup>[32,33]</sup> for homoallylic couplings. The only difference is that the intermediate antibonding orbital for  ${}^3J_{\text{C}_4\text{H}_1}$  is of the  $\sigma^*$ -type, while in homoallylic couplings they are of the  $\pi^*$ -type.

Resorting to a rather loose but pictorial expression, it can be said that results reported in this communication suggest that the present rationalization can be described in the following terms. Both for  $\sigma_{\text{C}_1\text{–C}_7} \rightarrow \sigma^*\text{C}_2=\text{O}$  and  $\sigma_{\text{C}_1\text{–C}_7} \rightarrow \pi^*\text{C}_2=\text{O}$ , hyperconjugative interactions can be thought of as a 'leak' of the FC spin information for both three-bond contributions to  ${}^3J_{\text{C}_4\text{H}_1}$  and  ${}^3J_{\text{C}_1\text{H}_4}$  couplings. However, owing to the  $\sigma_{\text{C}_3\text{–C}_4} \rightarrow \sigma^*\text{C}_2=\text{O}$  interaction, the former coupling,  ${}^3J_{\text{C}_4\text{H}_1}$ , 'recovers' the best part of the 'lost' FC spin information increasing the efficiency of its four-bond contribution, defining the asymmetry between these two  ${}^3J_{\text{CH}}$  couplings in norbornanone derivatives.

**Table 2.** Dihedral angle ( $^\circ$ ), bond angle ( $^\circ$ ), and main hyperconjugative interactions ( $\text{kcal mol}^{-1}$ ) for norbornanone and norborneol derivatives

Parameters	( <b>1</b> )	( <b>2</b> )	( <b>3</b> )	( <b>4</b> )	( <b>5</b> )	( <b>6</b> )	( <b>7</b> )
$\phi_{\text{C}_1\text{–C}_7\text{–C}_4\text{–H}_4}$	180	180	179	180	179	179	180
$\phi_{\text{C}_4\text{–C}_7\text{–C}_1\text{–H}_1}$	179	178	179	177	178	179	180
$\angle_{\text{C}_1\text{–C}_2\text{–C}_3}$	105	105	105	105	105	103	102
$\angle_{\text{C}_4\text{–C}_3\text{–C}_2}$	102	102	103	102	103	103	103
$\sigma_{\text{C}_1\text{–C}_7} \rightarrow \pi^*\text{C}_2=\text{O}$	2.2	2.3	1.9	2.2	2.0	–	–
$\sigma_{\text{C}_1\text{–C}_7} \rightarrow \sigma^*\text{C}_2=\text{O}^a$	3.8	3.9	4.0	3.8	4.0	Not observed	4.3
$\sigma_{\text{C}_3\text{–C}_4} \rightarrow \sigma^*\text{C}_2=\text{O}^a$	4.8	4.2	4.2	4.5	4.4	1.1	1.4

<sup>a</sup> For compounds **6** and **7** this corresponds to the interaction with the  $\sigma^*\text{C}_2\text{–O}$  antibonding orbital.

The same rationalization introduced above can be invoked to explain the behavior of  ${}^{3,4}J_{\text{C}_2\text{H}_7}$  and  ${}^{3,4}J_{\text{C}_3\text{H}_7}$  couplings in norbornanone determined experimentally by Parella *et al.*<sup>[34]</sup> In the former coupling, it is expected that the large  $\sigma_{\text{C}_1-\text{C}_7} \rightarrow \sigma^*_{\text{C}_2=\text{O}}$  and  $\sigma_{\text{C}_3-\text{C}_4} \rightarrow \sigma^*_{\text{C}_2=\text{O}}$  hyperconjugative interactions should increase notably its contribution transmitted by its four-bond coupling pathway. This effect should not be present in the latter coupling. The respective calculated values are 10.5 and 5.2 Hz, which are in excellent agreement with experimental values, 10.0 and 5.5 Hz, respectively. Similar effects are expected to be important in other cyclic compounds containing a carbonyl moiety, such as, for instance, adamantane and pinane derivatives.<sup>[35,36]</sup> In a forthcoming full paper, such effects are expected to be discussed in detail.

Taking into account that a  $\sigma^*(\text{C}=\text{C})$  antibonding orbital is a notable poorer acceptor than a  $\sigma^*(\text{C}=\text{O})$  antibonding orbital,<sup>[37]</sup> it can be expected that in camphene derivatives the asymmetry between  ${}^{3,4}J_{\text{C}_4\text{H}_1}$  and  ${}^{3,4}J_{\text{C}_1\text{H}_4}$  couplings is less marked than in norbornanone derivatives. In fact, this trend was observed by Parella *et al.*<sup>[34]</sup>

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