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Experimental Evidence for the Breakdown of the Karplus Relationship for $^3J(^{13}C, ^1H)$ in $^1H—C—C{=}^{13}C$ Systems

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Vicinal ^{1}H, ^{13}C coupling constants were measured for rigid unsaturated ^{1}H—C—C=^{13}C molecular frameworks at natural abundance. As a general trend, an empirical range of 4.5–6.5 Hz is observed independent of the value of the dihedral angle between the CH bond and the plane of the double bond. Furthermore, through-bond and through-space substituent effects also influence the magnitude of the coupling constants in a similar way to that known for saturated systems. In summary, two different additive transmission mechanisms take part in these coupling paths depending on the orientation of the π-system with respect to the allylic bond. The experimental evidence presented demonstrates the breakdown of the Karplus rule in this particular structural fragment.

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INTRODUCTION

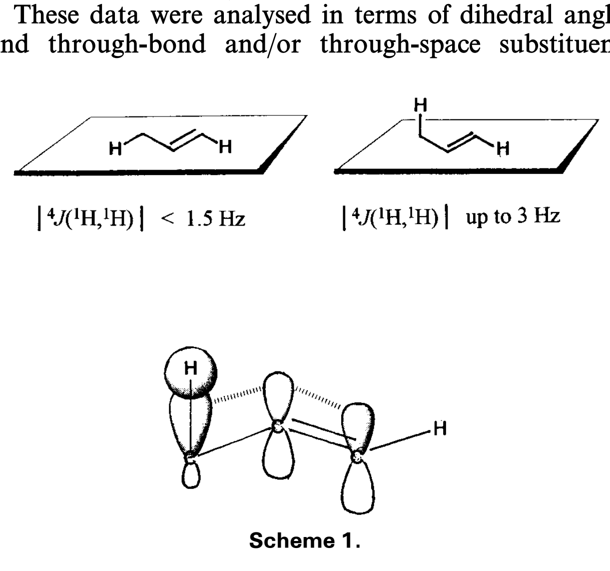
Long-range ^{1}H, ^{13}C couplings constants ($^nJ_{CH}$, $n > 1$) can be used as an alternative tool for structural and stereochemical analysis[1] when the information derived from other more conventional NMR parameters, such as ^{1}H, ^{1}H coupling constants or NOE effects, are not sufficient to solve the particular problem. Of the coupling constants, the vicinal ones ($^3J_{CH}$) are the most often used because of their Karplus relationship with the dihedral angle.[1] In this case, the overlapping effect of the σ-bond orbitals are the dominant factor to be considered and, therefore, maximum values of $^3J_{CH}$ are expected for dihedral angles about 0° and 180°.

It is known that the heteronuclear ^{1}H, ^{13}C *trans* coupling is generally greater than the *cis* coupling in ^{1}H—C=C—^{13}C systems,[2] as in the case of equivalent ^{1}H, ^{1}H systems, and this trend can be used in configurational studies of substituted alkenes. Here, the orientation of the π-bond does not influence the magnitude of the coupling because of the coplanarity of the whole system. However, in other olefinic systems, the π-bond orientation is an essential feature to be considered as, for instance, it is known that the magnitude of $^4J_{HH}$ in ^{1}H—C$_a$—C$_b$=C$_g$—^{1}H systems is larger if the allylic ^{1}H—C$_a$ bond is perpendicular to the olefinic plane[3] (Scheme 1).

A theoretical study on propene[4] proposed a breakdown of the Karplus relationship for this heteronuclear ^{1}H—C—C=^{13}C system. A maximum coupling constant of 11.5 Hz for a perpendicular orientation and minimum values of 5.2 and 8.3 Hz for coplanar *syn* and *anti* dispositions, respectively, were calculated. However, the theoretical resulting average value (9.0 Hz) is greater than the experimental value (6.7 Hz),[5] confirming the over-estimation of the π-mechanism in these theoretical calculations.

Only a few experimental values have been published for the ^{13}C, ^{1}H scalar interaction in the ^{1}H—C—C=^{13}C fragment, namely for butadienes,[6] cyclobutenes,[7] propenyl, isopropenyl, butenyl and isobutenyl derivatives[8] and some naturally occurring compounds, such as *cis*-verbenol,[9] α-pinene and α-carene.[10] Most of these data include non-rigid systems, which makes it more difficult to find a clear empirical relationship between $^3J_{CH}$ values and dihedral angles. In order to understand the transmission mechanisms operating in these ^{1}H—C—C=^{13}C systems, we present here extensive experimental $^3J_{CH}$ data for several rigid organic compounds obtained at natural abundance, including cyclohexene, norbornene, adamantane and pinene derivatives (Scheme 2).

These data were analysed in terms of dihedral angle and through-bond and/or through-space substituent



Scheme 1.

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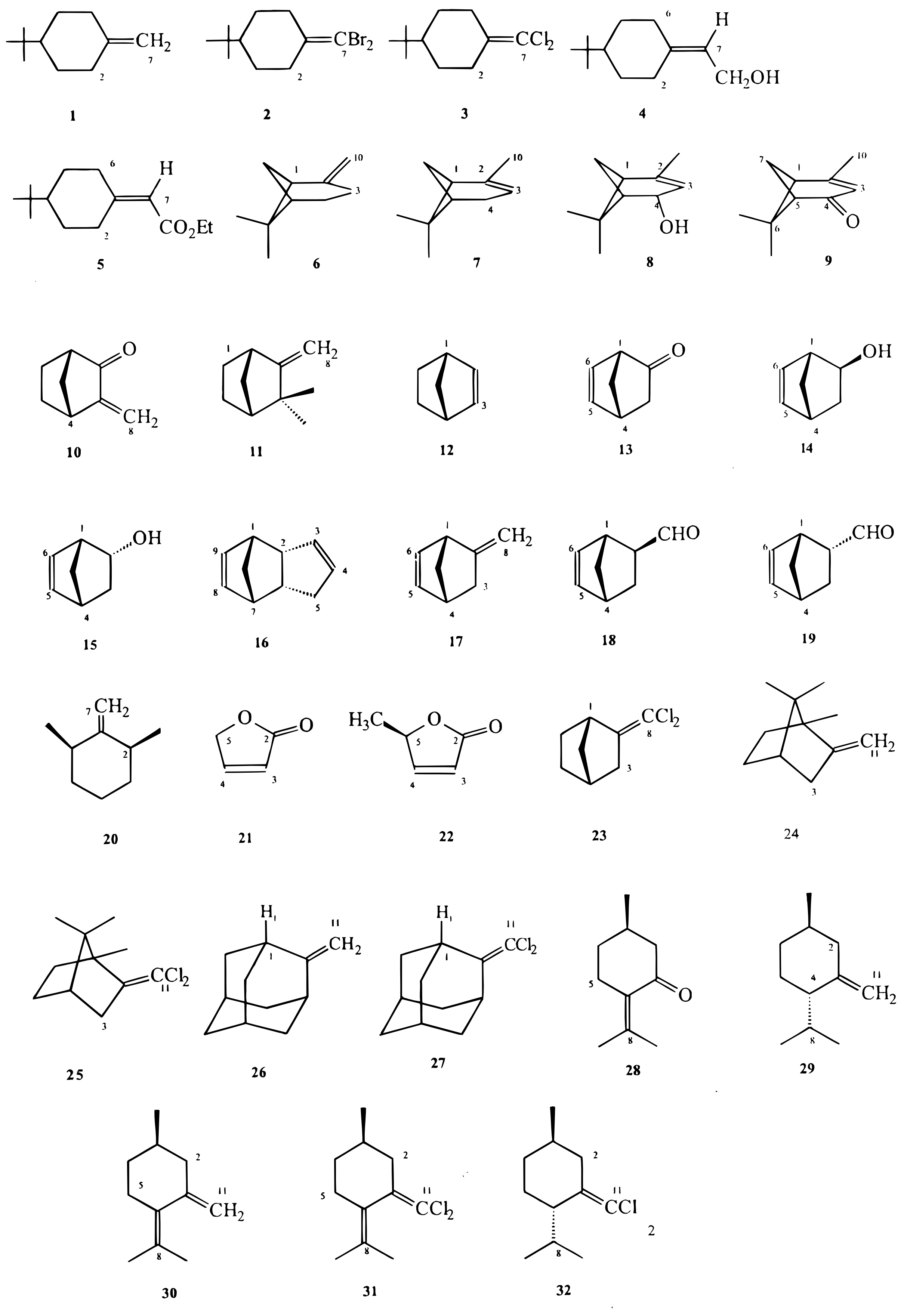
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CCl2
27
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28
CH2
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CH2
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CCl
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Scheme 2.

Table 1. Experimental $^3J_{CH}$ values and theoretical dihedral angles for compounds 1–32

Compound	No.	Atoms	$^3J_{CH}$ (Hz)	Dihedral angle (°)
4-*tert*-Butyl-1-methylenecyclohexane	**1**	H-2$_{eq}$/C-7	5.2	1
		H-2$_{ax}$/C-7	5.1	116
4-*tert*-Butyl-1-dibromomethylenecyclohexane	**2**	H-2$_{eq}$/C-7	5.6	2
		H-2$_{ax}$/C-7	6.7	119
4-*tert*-Butyl-1-dichloromethylenecyclohexane	**3**	H-2$_{eq}$/C-7	6.3	1
		H-2$_{ax}$/C-7	7.6	119
2-(4-*tert*-Butylcyclohexylidene)ethanol	**4**	H-2$_{eq}$/C-7	3.4	0
		H-2$_{ax}$/C-7	5.0	117
		H-6$_{eq}$/C-7	5.7	0
		H-6$_{ax}$/C-7	5.6	117
Ethyl 2-(4-*tert*-Butylcyclohexylidene)ethanoate	**5**	H-2$_{eq}$/C-7	3.3	5
		H-2$_{ax}$/C-7	4.7	113
		H-6$_{eq}$/C-7	5.6	3
		H-6$_{ax}$/C-7	5.1	114
β-Pinene	**6**	H-1/C-10	5.0	16
		H-3/C-10	4.1	29
		H-3′/C-10	4.4	87
α-Pinene	**7**	H-1/C-3	4.2	176
		H-4/C-2	5.6	121
		H-4′/C-2	5.6	120
		Me10/C-3	6.2	
cis-Verbenol	**8**	H-1/C-3	4.4	176
		H-4/C-2	5.3	118
Verbenone	**9**	H-1/C-3	4.8	177
3-Methylenenorbornan-2-one	**10**	H-4/C-8	2.5	18
Camphene	**11**	H-1/C-8	2.7	19
Norbornene	**12**	H-1/C-3	4.9	158
5-Norbornen-2-one	**13**	H-1/C-5	5.8	160
		H-4/C-6	6.4	157
exo-5-Norbornen-2-ol	**14**	H-1/C-5	6.2	158
		H-4/C-6	6.6	158
endo-5-Norbornen-2-ol	**15**	H-1/C-5	6.3	158
		H-4/C-6	5.9	158
endo-Bicyclopentadiene	**16**	H-1/C-8	6.2	158
		H-2/C-4	5.2	119
		H-5/C-3	5.5	118
		H-5′/C-3	6.4	122
		H-7/C-9	6.5	158
5-Methylene-2-norbornene	**17**	H-1/C-5	6.2	158
		H-4/C-6	5.9	159
		H-1/C-8	2.5	19
		H-3$_{exo}$/C-8	3.1	64
		H-3$_{endo}$/C-8	2.8	60
exo-5-Norbornene-2-carboxaldehyde	**18**	H-1/C-5	6.1	158
		H-4/C-6	6.2	158
endo-5-Norbornene-2-carboxaldehyde	**19**	H-1/C-5	6.6	158
		H-4/C-6	5.9	158
cis-2,6-Dimethyl-methylenecyclohexane	**20**	H-2$_{ax}$/C-7	4.2	122
γ-Butyrolactone	**21**	H-5/C-3	3.6	116
β-Angelicalactone	**22**	H-5/C-3	3.1	115
2-Dichloromethylenenorbornane	**23**	H-1/C-8	2.8	22
		H-3$_{exo}$/C-8	6.1	66
		H-3$_{endo}$/C-8	4.2	56
2-Methylenecamphor	**24**	H-3$_{exo}$/C-11	3.9	63
		H-3$_{endo}$/C-11	3.0	59
2-Dichloromethylenecamphor	**25**	H-3$_{exo}$/C-11	5.6	64
		H-3$_{endo}$/C-11	4.7	58
2-Methyleneadamantane	**26**	H-1/C-11	4.8	0
2-Dichloromethyleneadamantane	**27**	H-1/C-11	5.6	0
Pulegone	**28**	H-5/C-8	4.5	0
		H-5′/C-8	4.7	118
Methylenementhone	**29**	H-4$_{ax}$/C-11	5.0	126
		H-2$_{eq}$/C-11	5.6	2
		H-2$_{ax}$/C-11	4.6	120
Methylenepulegone	**30**	H-2/C-11	4.8	9
		H-6/C-8	5.4	3
Dichloromethylenementhone	**31**	H-2$_{eq}$/C-11	6.3	11
		H-2$_{ax}$/C-11	4.8	128
Dichloromethylenepulegone	**32**	H-5/C-8	5.6	0
		H-2/C-7	5.9	4

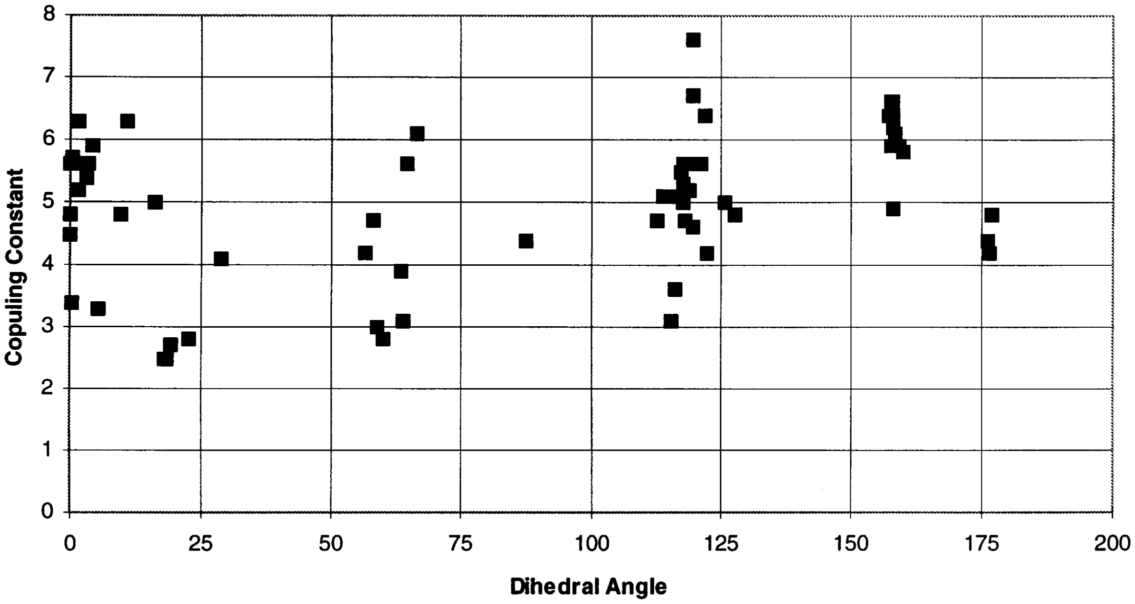

Figure 1. Trend of experimental data in Table 1.

dependence. Analysis of the results shows a breakdown of the Karplus relationship in these systems, preventing its application in stereochemical studies, and confirms the over-estimation of π-mechanism in the theoretical studies.[4] Similar theoretical and experimental results have been published for the equivalent $^{13}C—C—C=^{13}C$ systems in isotopically labelled compounds.[11]

RESULTS AND DISCUSSION

Table 1 shows experimental $^3J_{CH}$ data obtained for compounds **1–32** (Scheme 2) using different selective *J*-resolved 2D methods. If the coupled carbon was a protonated carbon we used the selective spin-flip method, inserting a refocused INEPT as a preparation period[9] in order to obtain a sensitivity improvement for the ^{13}C NMR signal due to this initial polarization transfer via $^1J_{CH}$. On the other hand, if a non-protonated carbon was the chosen one, we used the SDEPT-2D experiment[12] in which the polarization transfer is achieved directly by the $^nJ_{CH}$ coupling and the slow ^{13}C relaxation is therefore overcome.

Table 1 indicates that the magnitude of $^3J_{CH}$ in $^1H—C—C=^{13}C$ systems never approaches zero for any value of the dihedral angle. As a general trend, a $^3J_{CH}$ value in the range 4.5–6.5 Hz is observed (Fig. 1). This can be explained by taking into account the presence of two independent mechanisms which present similar contributions. First, there is a σ-electron mechanism operating as in saturated systems and showing maximum contributions around 5–7 Hz for dihedral angles near 0 and 180°, and minimum contributions (<1 Hz) if $\phi \approx 80–100°$. Examples of this are the H-1, C-5 and H-1, C-8 couplings in 5-methylene-2-norbornene (**17**) compared with those of saturated derivatives. Second, there is a π-electron mechanism arising from the interaction between the π-orbitals of the double bond and σ-orbital of the allylic C—H bond. This mechanism predominates when $\phi \approx 60–120°$ and is missing for dihedral angles near 0° and 180°. The maximum contribution is about 5 Hz for $\phi \approx 90°$ H-3′, C-10 in β-pinene (**6**). The same behaviour is also operative for the geminal coupling in the related $^1H—C—^{13}C=C$ and $^1H—C—^{13}C=O$ systems which have been studied recently.[13]

The effects of the nature, position and orientation of substituents present along the coupling pathway must also be considered. For instance, the α-substituent effect discussed by Van Beuzekom *et al.*[14] for saturated systems can be extended to unsaturated systems. As an example, comparison of the coupling data between the H-2_{eq} and H-2_{ax} protons with the exocyclic C-7 carbon in several substituted methylenecyclohexane derivatives (**1–5**) show that electronegative substituents at the α-carbon increase the magnitude of $^3J_{CH}$. Finally, through-space interactions must also be considered as in analogous saturated frameworks. For instance, the *exo* interaction in the C-2—C-3 fragment of the norbornane skeleton is 1–2 Hz larger than the *endo* interaction.[13] On the other hand, these interactions are similar in magnitude in norbornene systems owing to the proximity of the double bond on the other side of the molecule.[15]

CONCLUSION

The vicinal ^1H, ^{13}C coupling constants in $^1H—C—C=^{13}C$ systems result from the combination of two independent transmission mechanisms. The dihedral angle defined by the geometry of the bonds involved governs which of the two mechanisms dominates. Thus, if $\phi \approx 0°$ or 180°, the σ-electron mechanism operating as in analogous saturated systems predominates. On the other hand, for $\phi \approx 90°$ the π-electron mechanism predominates. In contrast to theoretical predictions which over-estimate the π-mechanism, a coupling value of 4.5–6.5 Hz is always observed for a substituent free coupling pathway. Clearly, the $^3J_{CH}$ coupling constants in $^1H—$

C—C=^{13}C systems can only be employed as a useful tool in conformational studies if a model compound with a closely related structure has been studied before.

EXPERIMENTAL

Except for the compounds described below, all compounds were purchased from Aldrich. The methylene derivatives **1**, **3**, **10**, **17**, **18**, **20**, **24**, **26**, **29** and **30** were obtained by Wittig reaction of the corresponding ketones and methyltriphenylphosphonium iodide following standard synthetic procedures. The dichloromethylene derivatives **3**, **23**, **25**, **27**, **31** and **32** were synthesized by a Wittig–Horner reaction using diethyl 1,1-dichloromethanephosphonate as a starting material.[16]

The dibromomethylenecyclohexane **2** was obtained from 4-*tert*-butylcyclohexan-1-one via reaction with a CBr_4–$(C_6H_5)_3P$ mixture.[17] The cyclohexylidenethanol and -ethanoate derivatives **4** and **5** were obtained by Wittig–Horner reaction of the 4-*tert*-butylcyclohexan-1-one with triethyl phosphonoacetate, followed by reduction with lithium aluminium hydride.[18]

All NMR experiments were performed on a Bruker AC-400 spectrometer equipped with a 5 mm QNP probe operating at 400.16 and 100.62 MHz for ^{1}H and ^{13}C, respectively. SPININEP and SDEPT-2D experiments were acquired as described in Ref. 12. The $^3J_{CH}$ data presented are accurate to ± 0.3 Hz. Structural data (i.e. dihedral angles) were obtained from force field calculations using the Allinger MM2 program.[19]

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