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Unusually large scalar coupling between geminal protons in a saturated pyrimidine

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Abstract

An unusually large geminal coupling has been observed in a stereochemically rigid system that permits a favorable coupling alignment between the methylene protons and an adjacent carbon-carbon double bond. Such couplings have been found to depend on both the alignment of a line connecting the geminal hydrogens and the nodal plane of the adjacent double bond, and the orientation of lone-pair electrons on adjacent heteroatoms. Electron withdrawal from *symmetrical* bonding orbitals results in more slightly positive geminal coupling constants while that from *antisymmetrical* bonding orbitals produces more negative coupling constants, which has been found to be very large in certain rigid systems.

KEYWORDS

^{1}H-^{1}H geminal couplings, sp^n hybridization, density functional theory calculations, double-bond nodal plane, hybridization, tetrahydropyrimidines

1 | INTRODUCTION

Pyrimidines and their derivatives are ubiquitous biomolecules found throughout nature. The well-known DNA bases, thymine and cytosine, and the RNA base, uracil, are pyrimidines,[1] and 1,2,3,4-tetrahydropyrimidines are a class of molecules that have been recently investigated for their antimicrobial and anti-inflammatory properties.[2,3] In their ongoing efforts to develop catalytic cycloaddition processes, the Doyle group reported the synthesis of 2-substituted 1,2,3,4-tetrahydropyrimidines **3** by a Lewis acid-catalyzed [4 + 2] aza-cycloaddition between azadiene **1** and aldimines **2** (Scheme 1).[4,5] This investigation was made possible by the discovery that enoldiazoacetates undergo rhodium-catalyzed reactions with aryl azides to form α-carbonylimines (**1**),[6,7] which undergo subsequent [4 + 2]-cycloaddition with imines to form pyrimidine

products (**3**) and whose generality was demonstrated in this report (PMP = *para*-methoxyphenyl, Tf = trifoliate (trifluoromethylsulfonyl), TBS = *tert*-butyldimethylsilyl).[5]

When a series of these tetrahydropyrimidines was studied by ^{1}H NMR spectroscopy, unusually large scalar coupling constants of *ca.* −17.5 Hz were observed between the geminal C6-hydrogens of **3**. We became interested in the conformational and stereoelectronic effects that could be responsible for this apparent anomaly.

Geminal ^{1}H-^{1}H coupling constants, which are almost always negative, are generally neglected with respect to vicinal couplings. Dutifully listed in NMR data tables, they are seldom an integral part of the discussions of NMR data. While a wealth of stereochemical information concerning the torsional-angle relationships of vicinally coupled protons can be derived from the Karplus relationship,[8] geminal coupling constants, by their very definition, provide no
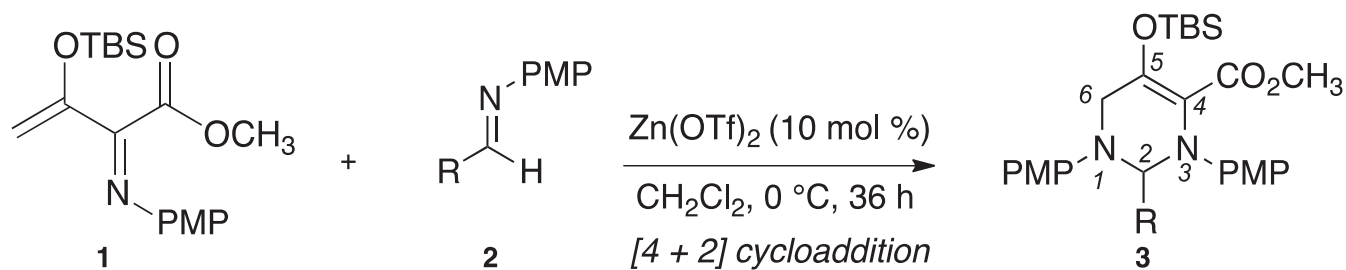
SCHEME 1 Synthesis of 1,2,3,4-tetrahydropyrimidines by a Zn^{2+}-catalyzed [4 + 2] cycloaddition[4,5]

analogous information. However, geminal coupling constants are quite sensitive to the electron density on the central carbon atom. This electron density is, in turn, influenced by four factors that could be important in the tetrahydropyrimidines under investigation: (i) the hybridization of the central carbon atom (ii) hyperconjugation of the C-H bonds with adjacent π-bonds, (iii) overlap of the C-H bonds with electron-pairs on adjacent heteroatoms, and (iv) inductive effects of adjacent electronegative substituents.[9]

Barfield and Grant demonstrated that the geminal coupling constants of methylene hydrogens adjacent to a carbon-carbon double bond could be predicted. Specifically, the authors found that the geminal coupling constants vary as a function of the torsional angle between an invisible "line" connecting the methylene hydrogens (in red) and the plane of the double bond (in blue, both in Figure 1).[10] For systems possessing rigid geometries, maximum effects producing negative coupling-constant increases of *ca.* −4.5 Hz, *that is,* even *more* negative coupling constants, are observed when the internuclear H-H line (a "through-space line" connecting the 2 geminal hydrogens) is orthogonal to the nodal plane (Figure 1a). When the H-H line is tilted at an angle of 60° with respect to the nodal plane (1 methylene hydrogen is parallel to the p-orbitals), smaller effects of *ca.* −2 Hz are detected (Figure 1b). In addition, a very small positive effect (>zero) on the coupling is found when the H-H line is tilted at an angle of 30° to the nodal plane (1 methylene proton is located in the nodal plane, Figure 1c), and a very small negative effect (<zero) is seen when this line is parallel to the plane (Figure 1d).

The tetrahydropyrimidine (**3**) under consideration is related to Figure 1 in the following manner. As the reader is sighting down the 5,6-single bond, the double-lobed

p-orbital of C-5 is vertical and perpendicular to the horizontal 4,5-nodal plane (in blue). An imaginary line connecting the 6-methylene hydrogens is also shown in red. The 6-geminal hydrogens are then rotated in 30° increments from an orthogonal orientation (a) to a parallel orientation (d) of the C-5 p-orbital with respect to the 4,5-nodal plane as described above.

In addition, smaller effects have been observed for oxygen, nitrogen, and sulfur atoms that are adjacent to methylene groups. Two effects are in play with N-1 of the tetrahydropyrimidines: σ-withdrawal by the electronegative N-1 and π-donation of its lone-pair electrons, and they work in concert to make the geminal coupling slightly less negative by *ca.* 0.5 Hz in the case of nitrogen.[9,11,12]

Pople and Bothner-By[13,14] have investigated the correlation of magnitude and sign of ^1H-^1H coupling constants with molecular structure. They found that valence bond and, even better, molecular orbital theory explain coupling-constant trends due to both different substituents and hybridization. They proposed that formation of suitable linear combinations consisting of (i) hydrogen $1s$ functions and (ii) wave functions corresponding to two π-bonding orbitals of carbon permits construction of the following four molecular orbitals, ψ_1-ψ_4:

1. ψ_1: symmetric bonding
2. ψ_2: antisymmetric bonding
3. ψ_3: symmetric antibonding
4. ψ_4: antisymmetric antibonding

In the ground state, 2 electrons are placed in each of the lowest energy orbitals, ψ_1 and ψ_2. Spin coupling between the 2 hydrogens involves separate contributions from the

(A) (B) (C) (D)
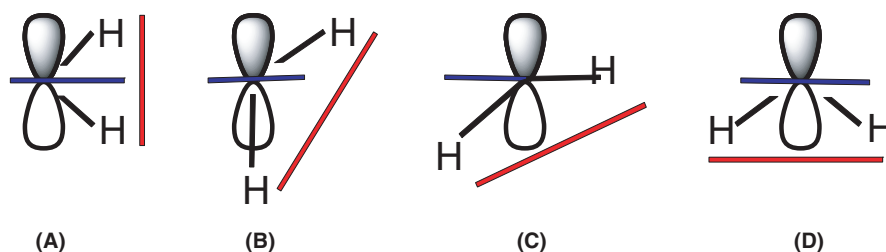
FIGURE 1 A-D: Barfield-Grant diagram

electron pairs in ψ_1 and ψ_2 in which the magnitude and sign of the coupling constant depends on (i) the excitation energy to triplet states of the same symmetry (ψ_1 to ψ_3 and ψ_2 to ψ_4) and (ii) matrix elements that connect these states. Although calculations of the absolute magnitudes of the above contributions to coupling constants are certainly far from trivial, the following, *opposite* trends have been observed for the 2 types of electron withdrawal:

1. Withdrawal of electrons from *symmetric* bonding orbitals (ψ_1), generally inductive effects, results in the ^{1}H-^{1}H coupling constant becoming more *positive*.
2. Withdrawal of electrons from the *antisymmetric* bonding orbitals (ψ_2), generally hyperconjugative effects, results in the ^{1}H-^{1}H coupling constant becoming more *negative*.

2 | RESULTS AND DISCUSSION

The above (i) Barfield-Grant relationship,[10] relating geminal coupling constants of methylene hydrogens adjacent to carbon-carbon double bonds to the torsional angle of adjacent methylene hydrogens, provides information on the geometry of the molecule and (ii) Pople-Bothner-By correlation[13,14] of the sign and magnitude of geminal coupling constants relative to methane (-12.57 Hz)[15] for electron withdrawal from symmetric bonding orbitals (ψ_1) or antisymmetric bonding orbitals (ψ_2) furnishes a means of determining whether the withdrawal of electron density from symmetric or antisymmetric bonding orbitals is important. The very large, negative spin coupling constants (*ca.* -5 Hz more negative than that of methane[15]) that were observed for a series of four tetrahydropyrimidine

systems in which the aryl ring at position 2 bears the following *para*-substituents: H (-17.5 Hz), Br (-17.5 Hz), CH$_3$ (-17.4 Hz), and NO$_2$ (-17.6 Hz) indicate that (i) the molecular geometry of the tetrahydropyrimidines must be one in which a line connecting the geminal hydrogens on C-6 is perpendicular, or very close, to the nodal plane of the tetrahydropyrimidine 4,5-double bond (Figure 1a) and that (ii) substantial electron withdrawal from antisymmetric bonding orbitals is important in these systems.

Structure elucidation of compound **3** by ^{1}H and ^{13}C NMR revealed both a 4,5-double bond and an aryl-amino nitrogen on adjacent sides of the geminal 6-protons.[4,5] The lone-pair electrons of N-1 could make the above geminal coupling constants slightly more positive (*ca.* 0.5 Hz) if they were oriented in an antiperiplanar or eclipsed arrangement to either H-6a or H-6b.[9,11,12] However, molecular models indicate that while eclipsed orientations are more likely than antiperiplanar arrangements, they are still 20°-30° removed from complete zero-degree orientations. It would thus appear that the effects of nitrogen-lone pair electrons on the coupling of the above geminal hydrogens are very small, perhaps approximately +0.5 Hz.

This view is also supported by more recent work of Zhu et al., who have examined a large series of tetrahydropyrimidines in which N-1 has both alkyl and 4-substituted aryl groups. They found that *both* types of substituents resulted in H-6a/H-6b geminal coupling constants in the range of -17.6 to -18.0 Hz.[16]

We have used Density Functional Theory (DFT) calculations[17] (MPW1PW91 and B3LYP functionals) to elucidate the structural and electronic features of the nature of the tetrahydropyrimidine ring system that lead to large germinal couplings. After an exhaustive conformation search, we located structure A as the lowest energy conformer.
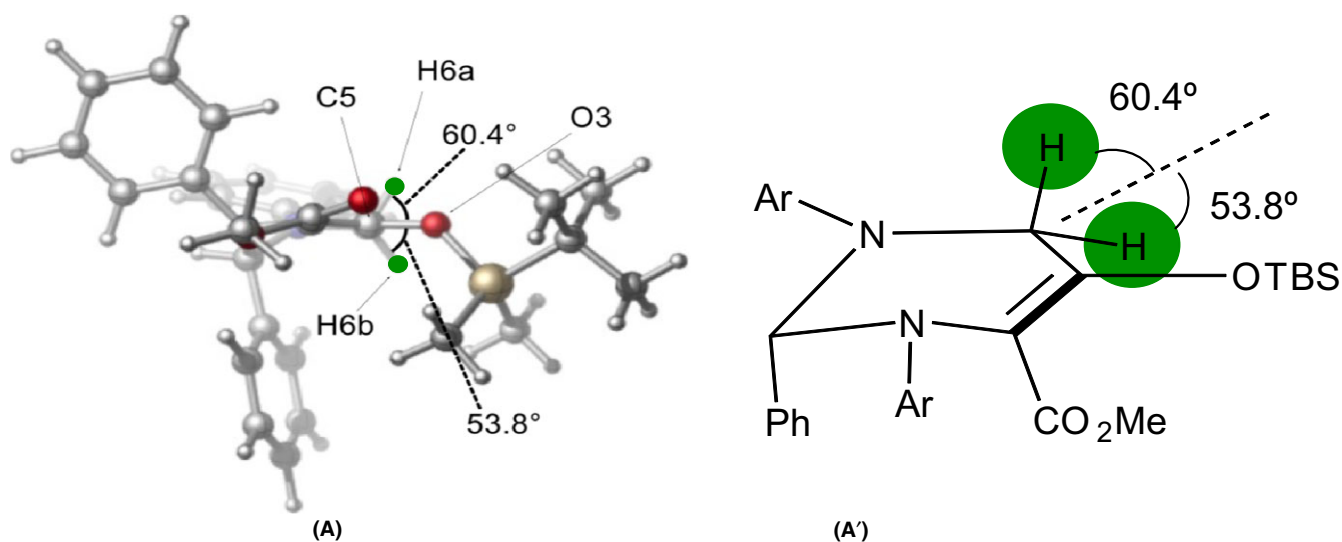
FIGURE 2 Lowest-energy structure (B3LYP/6-31G(d)) using Ar = Ph as a model system. Real system is Ar = anisole

Notably, the lowest energy structures differ concerning rotation of the CO_2Me group with respect to the $C-CO_2Me$ bond. All other conformers were found much higher in energy (>5 kcal/mol) and, therefore, are not expected to contribute significantly to the *J*-coupling in solution.

As shown in Figure 2, DFT calculations, indeed, show that the orientation of the H-6a/H-6b "line" is very close to perpendicular to the nodal plane of the C4=C5 double bond. Specifically, the torsional angles from the two geminal hydrogens (green) to the C-O bond (in the same plane as the C=C bond) are nearly identical, and the magnitudes deviate by only *ca.* 5°-7° from H-H line being perpendicular to the C=C bond. Notably, these calculations also demonstrate that N-1 is basically in the *same* plane of the tetrahydropyrimidine as are N-3, C-4, C-5, and C-6. Torsional angles for the planar C6-C5=C4-N3 system are 5.33° (MPW1PW91/6-311G(d)) and 5.54° (B3LYP/6-311G (d)), while those for N1-C6-C5=C4 are comparable at 4.03° (MPW1PW91/6-311G(d)) and 3.52° (B3LYP/6-311G (d)). Conversely, C-2 is *out* of the ring plane as demonstrated by the torsional angles for the N3-C2-N1-C6 fragment of 63.28° (MPW1PW91) and 62.07° (B3LYP).

TABLE 1 Calculated and observed $^2J_{H6a,H6b}$ values

	MPW1PW91[a]	B3LYP[a]
(1) Fermi contact:	−18.390	−17.508
(2) Diamagnetic spin orbit:	−0.117	−0.161
(3) Paramagnetic spin orbit:	0.028	0.057
(4) Spin Dipolar:	0.400	0.382
Total (calculated):	−18.079 Hz	−17.229 Hz

[a]Calculated using a 6-311G(d) basis set.
Experimental: −17.5 Hz.

TABLE 2 Typical $^2J_{HH}$ values for various sp^n values

Hybridization	$^2J_{HH}$
(1) sp^2	+2.5 Hz
(2) $sp^{2.5}$	−4 Hz (cyclopropanes)
(3) sp^3	−12.6 Hz
(4) $sp^{3.38}$ (average)	−17.5 Hz

Note that the C_6-H_A and C_6-H_B hybridizations are $sp^{3.31}$ and $sp^{3.44}$, and the calculated $H_A-C_6-H_B$ angle is 107°.

TABLE 3 Observed and calculated ^{13}C chemical shifts

	Observed	MPW1PW91	B3LYP
(1) C-2	78.5	79.69	81.14
(2) C-4	118.9	118.72	120.65
(3) C-5	147.8	159.18	159.97
(4) C-6	47.8	47.68	48.35

DFT calculations provide additional information on these tetrahydropyrimidine systems. The calculated $^2J_{H6a,H6b}$ is dominated, as expected, by the Fermi contact mechanism, and various contributing terms are given in Table 1.

Fermi interactions are also proportional to the product of the *s*-character of the two C-H bonds, which are shown in Table 2.

Calculated ^{13}C chemical shifts agree fairly well with observed shifts with the exception of C-5.

3 | CONCLUSION

In those situations where molecular geometry is relatively rigid and the "H-H line" is orthogonal to the nodal plane of a carbon-carbon double bond, maximum geometrical effects occur, and geminal coupling constants of *ca.* −17.5 Hz and even *ca.* −21.5 Hz, for two properly aligned double bonds, can be observed. In systems such as these, substantial withdrawal of electrons from the antisymmetric bonding orbital (ψ_2) is very important and, together with a favorable geometry, results in the large observed, negative coupling constants.

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