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(8) K = (protein concentration in the upper phase)/(protein concentration in the lower phase).

(9) Dextran (M_w = 500 000)–poly(ethylene glycol) (M_w = 6000–7500) two-phase system of the total composition: dextran 7% (w/w), poly(ethylene glycol) 5% (w/w), water 88% (w/w).[4] This two-phase system is one of those most commonly used.

(10) Throughout this work a commercially available enzyme (Sigma, Type XII, 320 I.U.) was used without further purification; G-6-PDH and 6-phosphogluconate were assayed spectrofluorimetrically following the procedure reported by O. L. Lowry and J. W. Passonneau in "A Flexible System of Enzymatic Analysis", Academic Press, New York and London, 1972, pp 68 and 205; dextran (Sigma, M_w = 500 000), PEG (Polysciences, M_w = 7500), Ficoll (Sigma, M_w = 400 000), UCON 50 HB 5100 (Union Carbide, M_w = 5100) were used as purchased.

(11) The stability of the native enzyme in the Ficoll phase was good: its half-life was approximately 6 days at 25°. The catalytic activity of the enzyme in this medium was about 70% of its activity in an analogous solution prepared by omitting the organic polymer. In general, enzymes tolerate high concentrations of materials related to these polymers without loss of activity: J. J. O'Malley and R. W. Ulmer, *Biotech. Bioeng.*, **15**, 917 (1973); C. Toniolo, G. M. Bonora, and A. Fontana, *Int. J. Peptide Protein Res.*, **6**, 283 (1974); S. L. Bradbury and W. B. Jakoby, *Proc. Nat. Acad. Sci. U.S.A.*, **69**, 2373 (1972).

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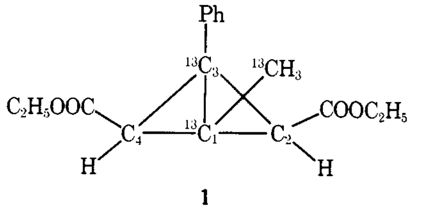
The Sign of the Bridgehead–Bridgehead $^{13}C-^{13}C$ Coupling Constant in a Bicyclobutane[1]

Sir:

Our interest in the chemical and physical properties of bicyclobutane and derivatives, coupled with our recent successful synthesis of diethyl 1-methyl-^{13}C-3-phenylbicyclo[1.1.0]butane-*1,3*-$^{13}C_2$-*exo,exo*-2,4-dicarboxylate (**1**) has allowed us to determine and herein report signs of several C–C and C–H coupling constants. The most significant of these is the bridgehead–bridgehead $^{13}C-^{13}C$ coupling constant which we now have determined to be *negative* by a series of off-resonance heteronuclear decoupling experiments as described below.



1

The interest in the sign of this coupling constant stems from the notion that this bond contains a very high degree of p character[3] and, as a result, should have a very small coupling constant. This derives from the assumed relationship between the Fermi contact contribution to the coupling constant and the product of the s character of the orbitals comprising the bond.[4] The first such postulated relationship (eq 1)[4] could not accommodate a negative coupling constant. Further refinement by Pople and Santry[5] led to the ability to predict negative coupling constants.

Table I.

Coupling constant[a]	Value	Coupling constant[a]	Value
$^1J_{C_1C_3}$	−5.4 ± 0.5 Hz	$^2J_{C_3C_M}$	−2.4 ± 0.5 Hz
$^1J_{C_1C_M}$	+53.2 ± 0.5 Hz	$^2J_{C_1H_M}$	−7.3 ± 0.5 Hz
$^1J_{C_MH_M}$	+129 ± 1 Hz	$^3J_{C_3H_M}$	+2.7 ± 0.5 Hz

[a] See text for explanation of subscripts.

$$^1J_{^{13}C-^{13}C} = 0.0550(\%S_A)(\%S_B)\ \text{Hz} \qquad (1)$$

This has not been useful, however, because it requires knowledge of energies and wave functions of excited states. Recent developments in spin–spin coupling theory by Pople, McIver, and Ostlund[6] have eliminated this requirement. Using localized orbitals Schulman and Newton have derived eq 2[7,8]

$$^1J_{^{13}C-^{13}C} = 0.0621(\%S_A)(\%S_B) - 10.2(\pm 2.4)\ \text{Hz} \qquad (2)$$

and have predicted *negative* values for the bridgehead–bridgehead coupling constants in bicyclobutanes.[3b,7-9] Their perturbation calculations[7] show the negative value to be the result of small negative values of all three terms—the Fermi contact, orbital-dipole, and spin-dipolar contributions. In fact bicyclobutanes may be unique in this regard and might be the only compounds to show a negative $^1J_{CC}$.[7]

The observation of a negative $^1J_{CC}$ therefore is consistent with the idea of a negative Fermi contact term and a high degree of p character in the bridgehead–bridgehead bond. From eq 2, the value of −5.4 Hz for $^1J_{CC}$, and the assumption that the C_1–C_3 bond in **1** is symmetrical, one can calculate that the carbon orbitals which make up this bond are hybridized $sp^{10.4}$.

Table I lists the appropriate coupling constants,[2] including signs, as determined by the method of off-resonance heteronuclear decoupling. We will designate the nuclei as: C_3, C_1, C_M (methyl carbon), and H_M (hydrogens on the methyl group). All signs are relative to the C_M–H_M sign which is taken as positive.[10]

The carbon magnetic resonance spectrum of **1** consisted of overlapping spectra of triply labeled material, three types of doubly labeled material, and three types of singly labeled compound. This was a result of 90% ^{13}C labeling in C_1 and C_3 and 65% ^{13}C labeling in C_M.[2] In addition the proton spectrum of the methyl group similarly showed overlapping spectra due to these same molecules.

The off-resonance heteronuclear decoupling technique utilized extensively by Jakobsen and co-workers[11] has subsequently been used successfully to obtain the relative signs of $^{13}C-^{31}P$ and $^{31}P-^1H$ coupling constants.[12] Our experiments involved irradiating the protons at various frequencies in steps as small as 4 Hz around the selective decoupling condition while observing the ^{13}C spectrum. The observations consisted of noting that, for example, low frequency proton irradiation enhanced the low frequency ^{13}C doublet of C_1 whereas high frequency proton irradiation enhanced the high frequency ^{13}C doublet of C_1 (in the triply ^{13}C labeled material). This requires that $^1J_{C_1C_M}$ and $^1J_{C_MH_M}$ have the same sign; that is, since $^1J_{C_MH_M}$ is positive, so is $^1J_{C_1C_M}$. The ^{13}C doublet due to C_1, where C_1 and C_3 are labeled, showed the high frequency ^{13}C peak enhanced at lower proton frequency whereas the low frequency ^{13}C peak was enhanced at high frequency proton irradiation. Thus $^1J_{C_1C_3}$ and $^3J_{C_3H_M}$ have opposite signs. By observation of the methyl carbon atom we could determine similarly that $^1J_{C_1C_M}$ and $^2J_{C_1H_M}$ are of opposite sign and $^2J_{C_3C_M}$ and $^3J_{C_3H_M}$ are also of opposite sign. Because of the small couplings of C_3 to the aromatic hydrogens resulting in broad peaks we were not able to use this technique further.

By observing the methyl proton double-doublet due to labeling at C$_1$ and C$_3$ only, and irradiating the carbon frequencies in steps from 20 to 2 Hz, we could demonstrate that $^3J_{C_3H_M}$ and $^1J_{C_1C_3}$ have opposite signs, the same result as above. More importantly, however, $^1J_{C_1C_3}$ and $^2J_{C_1H_M}$ were shown to have the same sign by noting that low frequency carbon irradiation enhanced the low frequency proton peak whereas higher frequency irradiation enhanced the high frequency proton peak. Thus the signs are uniquely determined (based on $^1J_{C_MH_M}$ being positive[10]).

It should be noted also that placing the ^{13}C irradiating frequency to a position 5 ppm more shielded than that carbon decoupling frequency needed to reduce the proton double-doublet of C$_1$–C$_3$ dilabeled material to a doublet (J = 7.3 Hz) results in another doublet (J = 2.7 Hz). This means the less shielded carbon, C$_3$ (29.02 ppm from TMS),[2] is coupled to H$_M$ with the smaller J while the more shielded carbon, C$_1$ (24.02 ppm),[2] is coupled to H$_M$ by the larger J.

Finally, since little is known about the signs of carbon-carbon coupling constants[13] except that $^1J_{CC}$ is positive[5,14,15] (with the exception of $^1J_{C_1C_3}$ in bicyclobutane) it would be inappropriate to discuss the significance of a negative $^2J_{C_3C_M}$. It should also be noted that as expected,[10c] the signs of $^1J_{CH}$, $^2J_{CH}$, and $^3J_{CH}$ alternate. In addition the sign of $^2J_{CH}$ is expected to be negative for a system where the H is attached to an sp^3 hybridized C which in turn is bonded to either an sp^2 or sp hybridized C,[16] which is the case in a 1-methylbicyclobutane.[3a]

We would also like to point out that all of the signs and values for the coupling constants reported agree in sign and approximate value with those calculated by Schulman in 1-methylbicyclobutane using the INDO coupled Hartree-Fock approxmation.[17]

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Lack of Selectivity in the Electrophilic Addition of *p*-Toluenesulfonylnitrene to Tertiary Amines. Conformational Equilibrium in *N*-Methylpiperidines

Sir:

The position of the *N*-methyl equilibrium in *N*-methylpiperidines (**1** $\rightleftharpoons$ **2**) is a problem of considerable current interest.[1-3] We report some results obtained by a novel photochemical procedure, the rationale of which has been outlined previously.[4]

p-Toluenesulfonylnitrene, p-MeC$_6$H$_4$SO$_2$N, photochemically generated in situ from the azide, was shown[4] in competition experiments not to discriminate between dimethyl sulfide and diisopropyl sulfide in the reaction to produce iminosulfuranes p-MeC$_6$H$_4$SO$_2$N$^-$S$^+$R$_2$, and we have now found a similar lack of discrimination between butyl- and isobutyldimethylamines in the competitive conversion into aminimides p-MeC$_6$H$_4$SO$_2$N$^-$N$^+$Me$_2$R. These quantitative comparisons (rate-constant ratio 1.0:1 in each case[5]) are supported by further examples of lack of selectivity of the nitrene probe for competitive additions to nucleophiles in systems where precise quantitative assessments are adventitiously more difficult. There appears to be little if any discrimination between dimethyl sulfide and di-*ter*-butyl sulfide despite the ready thermal conversion of the iminosulfurane from the latter into the sulfenamide p-MeC$_6$H$_4$SO$_2$NHSCMe$_3$ presumably because of internal steric compressions. Likewise, the nitrene adds about equally readily to each nitrogen atom of 1,2,4-trimethylpiperazine.[6] Our deductions in the sequel are based on the expectation, which accords with all our available experimental evidence, that *p*-toluenesulfonylnitrene will be kinetically unselective between tertiary piperidine conformers such as **1** and **2** or **5** and **6** in the reaction to yield diastereoisomeric aminimides.

From 1-methyl-4-*tert*-butylpiperidine (**1** $\rightleftharpoons$ **2**; R = equatorial 4-*t*-Bu) and the nitrene only one aminimide (formulated as **4**; R = equatorial 4-*t*-Bu) was observed by examination of the ^{1}H NMR spectrum of the appropriate product fractions. We were just able to detect 1% of the diastereoisomer **3** in the spectra of calibration mixtures,[7] 2% being very clearly evident. *We deduce that the 4-tert-butyl base and hence the parent N-methylpiperidine* (**1** $\rightleftharpoons$ **2**; R = H) *has no more than about 1% of the conformation* **1** *with axial N-methyl* ($-\Delta G^\circ_{300} \geqslant 2.7$ kcal mol^{-1} in CCl$_2$FCClF$_2$)[8]. 1,4-Dimethylpiperidine and the nitrene gave mixed diastereoisomeric imides in ratio 22:1, a value we interpret in terms of two predominating conformers **2** (R = equatorial 4-Me) and **2** (R = axial 4-Me) in the reactant base, in ratio controlled by the 4-methyl conformational preference, which is presumably similar to that[10] of methyl-