Substituent Effect on Geminal Coupling Constants in Allylic Methylene Groups

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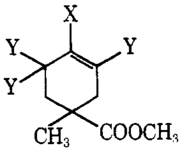
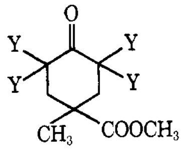
Abstract: The geminal proton–proton coupling constants have been determined for the allylic methylene protons in a series of selectively deuterated cyclohexene derivatives. The effect of substituents β to the methylene group on ^2J is found to agree with theoretical calculations. Electron-withdrawing substituents cause a negative shift and electron-donating substituents cause a positive shift in ^2J, the total variation being 2.9 Hz. This effect is larger than that exerted by para substituents in benzylic systems as would be expected for a more polarizable double bond. The ^2J's correlate poorly with the existing substituent parameters but correlate well with the shift of the olefinic protons adjacent to the double bond. This correlation is interpreted as evidence that the change in ^2J is produced primarily by a resonance interaction of the substituent with the double bond resulting in a change in the hyperconjugative withdrawal of electrons from the adjacent methylene group.

In the application of proton magnetic resonance to the elucidation of structural and stereochemical problems use of the geminal coupling constant (^2J) has lagged behind that made of the vicinal coupling constant (^3J). Theoretical calculations of geminal coupling constants by VB[1] and MO[2,3] methods have explained numerous reported variations in ^2J with structure[4] and have postulated[2,3] several additional structural influences on ^2J. One such influence, the effect of the orientation of lone pairs on adjacent atoms, has been confirmed by extensive experimental evidence.[5] A second important factor, the effect of a π bond on ^2J in the adjacent methylene group, has been less thoroughly examined. All three theoretical treatments predict that the π bond will exert an influence which is orientation dependent, causing a negative shift[6] in ^2J which is largest when the H–H axis of the methylene group is parallel to the π orbital. A projected angle ϕ is defined to be zero in this conformation. The predictions differ in that the effect on ^2J, in the conformation produced by a 90° rotation about the CH_2—C= bond, is calculated to be negative,[1] zero,[2] and positive[3] by the three methods. In Figure 1 the qualitative predictions of theory are portrayed. Quantitatively the negative shift in ^2J may follow the relation,[2] $\Delta J = k \cos^2 \phi$, where ΔJ is the contribution to ^2J resulting from the hyperconjugative effect of the π bond, and k is a constant which has been estimated to be 4 Hz.[4] Investigations in our laboratory have attempted to obtain experimental evidence regarding the stereochemical dependence of this effect in a benzyl group. It has been shown that the effect of para substituents on ^2J in benzylic systems of the type $X\text{–}C_6H_5CH_2Z$ (in chiral molecules) correlates with their Hammett substituent constants.[7] More recently evidence has been presented[8] to show that the slope ρ of this ^2J–σ_p correlation is conformationally dependent as predicted by theory. It was found that in conformationally rigid systems[9] ρ changed from -1.9 for $\phi = 0°$ to $+0.2$ for $\phi = 90°$. We have now extended the investigation of substituent effects on ^2J to allylic systems. In this paper we describe the synthesis and nmr spectral properties of a series of cyclohexene derivatives whose geometry is such that the predicted effect should be nearly maximal (*vide infra*).

For the above purpose a series of allyl derivatives having three specific structural features is required. The molecules must contain an asymmetric center in order for ^2J to be measurable; they must provide spectra sufficiently simple to allow an accurate determination of ^2J; and they ought to be capable of synthesis by reasonably simple methods. One such series of compounds which possesses these requirements has the general formula **1**. The identity of X in the nine compounds studied can be seen in Table I. The necessity for three deuterium atoms in **1** is dictated by the requirement for spectral simplicity in their nmr spectra. In point of fact we have synthesized all members of series **2** as well as those of **1**. All members of series **1** are readily prepared from the deuterated ketone **3**. Similarly members of series **2** are prepared from **4**,[10] and **4** is readily transformed to **3** by aqueous base-catalyzed deuteration followed by reesterification.



1, **a–i**, Y = D
2, **a–i**, Y = H



3, Y = D
4, Y = H

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[1] M. Barfield and D. M. Grant, *J. Amer. Chem. Soc.*, **85**, 1899 (1963).

[2] J. A. Pople and A. A. Bothner-By, *J. Chem. Phys.*, **42**, 1339 (1965).

[3] G. E. Maciel, J. W. McIver, N. S. Ostlund, and J. A. Pople, *J. Amer. Chem. Soc.*, **92**, 4151 (1970).

[4] R. Cahill, R. C. Cookson, and T. A. Crabb, *Tetrahedron*, **25**, 4711 (1969), and previous papers in the same series.

[5] R. Cahill, R. C. Cookson, and T. A. Crabb, *ibid.*, **25**, 4681 (1969).

[6] The geminal coupling constant has been shown to be negative in sign for methylene protons at an sp^3 hybridized carbon atom in a variety of structures including a benzyl group: R. R. Fraser, R. U. Lemieux, and J. D. Stevens, *J. Amer. Chem. Soc.*, **83**, 3901 (1961); F. Kaplan and J. D. Roberts, *ibid.*, **83**, 4666 (1961); R. R. Fraser, *Can. J. Chem.*, **40**, 1483 (1962). It is assumed that ^2J is also negative in an allylic methylene group, and the substituent effects reported herein support this assumption.

[7] R. R. Fraser, P. Hanbury, and C. Reyes-Zamora, *Can. J. Chem.*, **45**, 2481 (1967); R. W. Franck and J. Auerbach, *ibid.*, **45**, 2489 (1967).

[8] R. R. Fraser and R. N. Renaud, *ibid.*, **49**, 755 (1971).

[9] R. R. Fraser and R. N. Renaud, *ibid.*, **49**, 746 (1971).

[10] M. Rubin and H. Wishinsky, *J. Amer. Chem. Soc.*, **68**, 338 (1946).

Table I. Nmr Spectral Parameters for Series **1**

Compound (X)	$-J_{\mathrm{AB}}$, Hz	$-J_{\mathrm{CD}}$, Hz	J_{AC}, Hz	J_{BD}, Hz	ppm from TMS δ_{A}	δ_{B}	δ_{C}	δ_{D}	δ_{v}[a]
1a (OCH_3)	16.4	13.2	1.25	0.79	2.59	1.96	2.03	1.66	4.51
1b ($N(CH_2CH_2)_2O$)	16.8	13.0	1.17	0.86	2.59	1.97	2.01	1.63	4.58
1c ($OCOCH_3$)	17.3	13.3	1.07	0.87	2.62	2.03	2.05	1.70	5.27
1d (Cl)	17.4	13.3	1.24	0.88	2.67	2.03	2.07	1.67	5.72
1e (H)	17.5	13.2	1.06	0.84	2.54	1.86	1.93	1.56	5.62
1f (C_6H_5)	18.1	13.2	1.11	0.92	2.73	2.10	2.10	1.73	6.06
1g ($CONH_2$)	18.8	13.4	1.20	0.79	2.73	2.05	2.03	1.63	6.61
1h ($COOCH_3$)	19.2	13.3	1.11	0.85	2.73	2.05	1.98	1.60	6.92
1i (CN)	19.3	13.4	1.23	0.73	2.74	2.03	2.02	1.61	6.56

[a] The chemical shift of the vinyl proton as measured on members of series **2** (0.1 *M* in $CDCl_3$).

These synthetic transformations, though by no means trivial from the practical point of view, all involve standard synthetic methods which need not be discussed. Details are provided in the Experimental Section.

One notable synthetic contribution, an alternate one-step synthesis of **2e** (X = H), has been achieved. Heating butadiene sulfone with methyl methacrylate gives a 59% yield of **2e**. We were also successful in developing an alternate preparation of **4** in four steps from butadiene sulfone and in an overall yield of 19%.[11]

Results

The 100-MHz spectra of **1** (a–i) were measured during simultaneous irradiation of the deuterium resonances to remove all effects of H–D coupling. Figure 2 shows the spectrum of **2i**, compared with that of **1i** (inset A), and an expanded version of the absorption due to the four protons in the cyclohexene ring (inset B). The protons give rise to two AB quartets, each line of which is further split into a doublet by long-range coupling. If we refer to the protons appearing from low to high field as H_A, H_B, H_C, and H_D,[12] H_A is weakly coupled to H_C (1.2 Hz) and H_B is weakly coupled to H_D (0.7 Hz). The geminal couplings J_{AB} and J_{CD} are 19.3 and 13.4 Hz, respectively. All coupling constants are equal to the observed splittings although exact AB analyses must be used to obtain the proton shifts. The results of analysis of the spectra of **1** (a–i) are presented in Table I.

Discussion

Conformational Properties of 1. Cyclohexene is known to exist in two equivalent half-chair conformations.[13] The derivatives **1a–i** will exist in two nonequivalent half-chair conformations, one with an axial carbomethoxyl, the other with an axial methyl. The position of the half-chair equilibrium depicted in eq 1 can be predicted from data available for the equilibrium between equatorial and axial conformers of 4-methylcyclohexene ($-\Delta G° = 1$–1.1 kcal/mol[14,15]) and 4-carbomethoxycyclohexene ($-\Delta G° = 0.84$ kcal/mol[16]). If the above effects are assumed to be additive in **1**, the half-chair form having an equatorial methyl group ought to be favored by 0.2–0.3 kcal/mol. The long-range coupling constants J_{AC} and J_{BD} provide experimental evidence on this point.

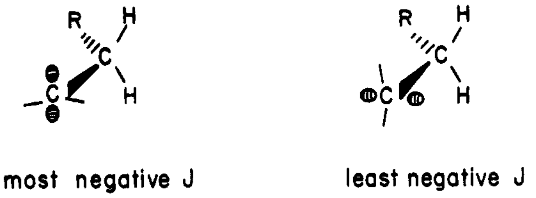
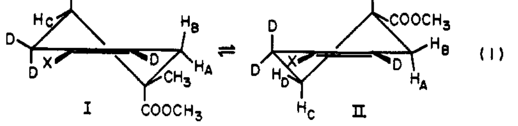


Figure 1. A three-dimensional representation of the conformations in which occur the maximum and minimum hyperconjugative interactions of a π bond with an adjacent methylene group.

It is well known that long-range coupling constants (^4J's) are largest when there is a W arrangement of the interacting nuclei.[17] Values of ^4J between diequatorial protons on a cyclohexane ring fall in the range of 1–2 Hz.[18] The coupling constants $^4J_{\mathrm{ae}}$ and $^4J_{\mathrm{aa}}$ are usually too small to be observable. Studies by Bystrov and Stepanyants[19] provide empirical relations which would estimate these couplings to be +0.2 ($^4J_{\mathrm{ae}}$) and −0.2 Hz ($^4J_{\mathrm{aa}}$). We need not estimate a value for $^4J_{\mathrm{ee}}$ in **1** but



(1)

only assume that $^4J_{\mathrm{aa}} = 0$. For the equilibrium 1 between the two half-chair forms I and II, $J_{\mathrm{AC}} = n_{\mathrm{I}}{}^4J_{\mathrm{ee}} + (1 - n_{\mathrm{I}}){}^4J_{\mathrm{aa}} = n_{\mathrm{I}}J_{\mathrm{AC}}$, where n_{I} represents the mole fraction of conformer I in the equilibrium. Similarly $J_{\mathrm{BD}} = n_{\mathrm{I}}{}^4J_{\mathrm{aa}} + (1 - n_{\mathrm{I}}){}^4J_{\mathrm{ee}} = (1 - n_{\mathrm{I}}){}^4J_{\mathrm{ee}}$. Thus $J_{\mathrm{AC}} + J_{\mathrm{BD}} = {}^4J_{\mathrm{ee}} = 2$ Hz and $n_{\mathrm{I}} = 0.6$ which corresponds to $\Delta G°_{30} = 0.25$ kcal/mol. In this way the long-range coupling data confirm the above estimate of the conformational equilibrium although they do not prove which conformer is preferred. The agreement between values of $\Delta G°$ derived from ^4J and from additivity is significant in that it provides evidence that **1** does not exist to any appreciable extent in the less stable boat form.[13] The fact that J_{AC} and J_{BD} remain constant

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(11) This route to **4** offers no improvement over the method of Rubin and Wishinsky,[10] and the reader is referred to the M.S. thesis of B. F. Raby, University of Ottawa, 1971, for details.

(12) In several members of series 1 the diastereotopic partner of H_A appears at slightly higher field than H_C. Nevertheless, we will refer to this proton as H_B in all cases.

(13) F. A. L. Anet and M. Z. Haq, *J. Amer. Chem. Soc.*, **87**, 3147 (1965).

(14) B. Rickborn, *J. Org. Chem.*, **30**, 2212 (1965).

(15) N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *J. Amer. Chem. Soc.*, **90**, 5773 (1968).

(16) N. S. Zefirov, V. N. Chekulaeva, and A. I. Belozerov, *Tetrahedron*, **25**, 1997 (1969).

(17) S. Sternhell, *Quart. Rev., Chem. Soc.*, **23**, 236 (1969).

(18) A. Rassat, C. W. Jefford, J. M. Lehn, and B. Waegell, *Tetrahedron Lett.*, 233 (1964).

(19) V. F. Bystrov and A. U. Stepanyants, *J. Mol. Spectrosc.*, **21**, 241 (1966).

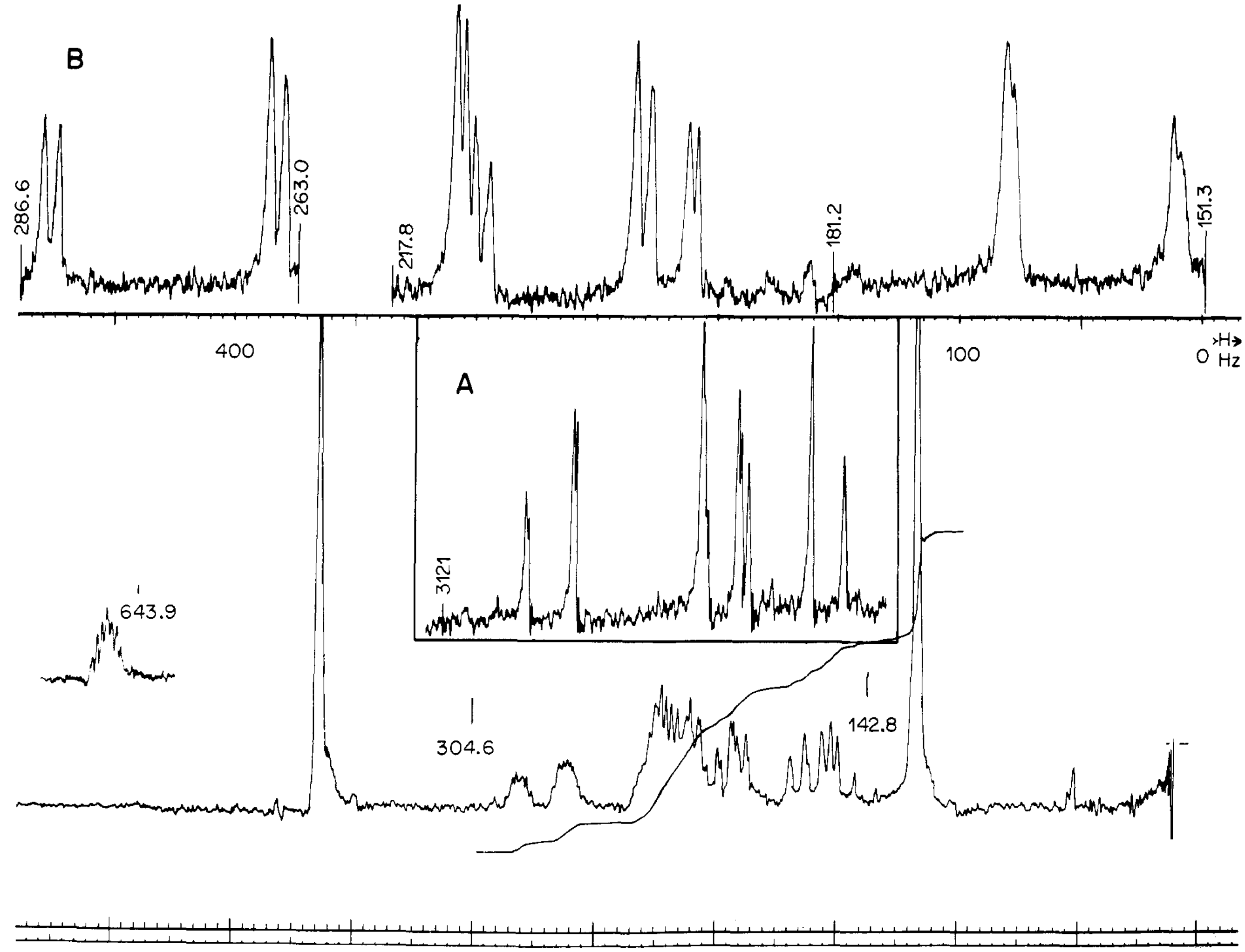

Figure 2. The 100-MHz pmr spectrum of **2i**. Inset A shows the absorption due to the ring protons in **1i** (1000 Hz sweep width), and inset B represents a fourfold expansion of this absorption. Both spectra were measured during simultaneous H–D decoupling.

throughout the series indicates that the variation in X does not alter the conformational equilibrium in **1a–i**.

With respect to the aims of this study the most significant conformational property of **1** is the orientation of the methylene protons at C-3 with respect to the π orbitals of the adjacent double bond. Electron diffraction studies[20,21] and theoretical calculations[15] both yield a value for ϕ of 15°.

Geminal Coupling Constants. The two geminal coupling constants J_{AB} and J_{CD} have quite different magnitudes. As seen in Table I, J_{AB} varies from 16.4 to 19.3 Hz in the series while J_{CD} remains essentially constant at 13.3 Hz. The larger size of J_{AB}, its variability, and the lower field shifts for H_A and H_B all indicate H_A and H_B to be the allylic protons at C-3. The 3-Hz variation in J_{AB} for different substituents is significantly larger than that caused by the same substituents in the para position of a series of benzyl derivatives[8] having a similar orientation angle, ϕ. The greater range of ^2J's in series **1** likely results from the fact that X causes a greater perturbation of the hyperconjugative ability of an isolated double bond than of a resonance stabilized aromatic ring. In both the benzylic and allylic systems a change in X which enhances hyperconjugative withdrawal of electrons from the methylene group produces a negative shift in ^2J. As in the benzylic systems there ought to be a correlation between the ^2J observed for a particular X and some substituent parameter of X. Previous investigators have reported that use of the Hammett substituent constant σ_p gave varying degrees of success in correlating substituent effects in olefins. Ionization constants[22] and reactivities[23] in two series of acrylic acids gave satisfactory[24] to excellent[24] correlations. Correlation of allyl halide solvolysis[25] reactions with σ_p were poor, however. Attempts to correlate the substituent effect on ^2J with σ_p gave poor results, the correlation coefficient being 0.823. An improved correlation can be obtained by plotting ^2J against the field and resonance parameters of Swain and Lupton.[26] Table II summarizes the correlations of ^2J showing that the best fit is obtained using $0.1\mathcal{F} + \mathcal{R}$ to represent the substituent

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(20) J. F. Chiang and S. H. Bauer, *J. Amer. Chem. Soc.*, **91**, 1898 (1969).

(21) H. J. Geiss and H. R. Buys, *Recl. Trav. Chim. Pays-Bas*, **89**, 1147 (1970).

(22) M. Charton and H. Meislich, *J. Amer. Chem. Soc.*, **80**, 5940 (1958).

(23) J. Hine and W. C. Bailey, Jr., *ibid.*, **81**, 2075 (1959).

(24) In a review article by H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953), the degree of correlation is arbitrarily defined by the correlation coefficient r; $r > 0.99$ is considered excellent, $r > 0.95$ is satisfactory, and $r > 0.90$ is a fair correlation.

(25) P. B. D. de la Mare, *J. Chem. Soc.*, 3823 (1960).

(26) C. G. Swain and E. C. Lupton, *J. Amer. Chem. Soc.*, **90**, 4328 (1968).

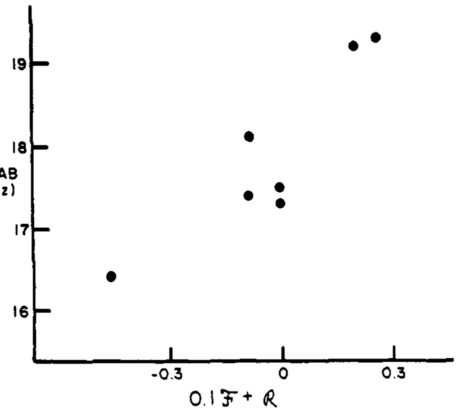

Figure 3. ^2J *vs.* $0.1\mathcal{F} + \mathcal{R}$.

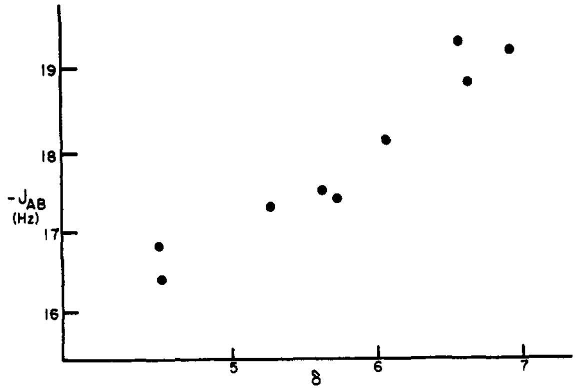

Figure 4. ^2J from series **1** *vs.* δ_v, the shielding of the proton at C-3 in series **2**.

parameter. A plot of ^2J against $0.1\mathcal{F} + \mathcal{R}$ is given in Figure 3. This improvement in the correlation by giving $\mathcal{R}$ more weight than $\mathcal{F}$ seems to indicate that a resonance effect has a greater influence on ^2J than on acid dissociation. The best correlation that we have been able to find is an empirical one. This is shown in Figure 4 which depicts a plot of ^2J *vs.* δ_v, the chemical shift for the vinyl proton at C-2 (as measured from the spectra of the members of series **2**). In this case the correlation coefficient is 0.962 and the standard deviation in J is 0.31 Hz. Undoubtedly this correlation of ^2J with δ_v stems from the presence of a common factor influencing both parameters.[27] A series of papers correlating the effects of substituents on vinyl proton shifts has recently appeared.[28] Shielding constants for over 30 substituents have been derived from a survey of the literature, and these are shown to have impressive predictive capabilities. Furthermore, the authors state that the majority of the olefinic proton shifts are best rationalized in terms of ground state mesomerism. This interpretation suggests that the common factor involved in the substituent effects on ^2J and δ_v is the resonance effect of the substituents. In summary, we conclude that the substituent affects ^2J primarily by its resonance interaction with the double bond. This interaction enhances or decreases the hyperconjugative withdrawal of electrons from the adjacent methylene group resulting in a negative or positive shift in ^2J as predicted by theory.[1,2] Theory also requires that the substituent effect be dependent upon ϕ, and this was proven to be so in benzyl systems. Since $\phi = 15°$ in series **1**, the observed substituent effect ought to be 93% of its maximum value ($\cos^2 \phi = 0.93$). Investigations of substituent effects on ^2J in allyl groups having different values of ϕ are in progress. It is hoped that these studies will determine the precise nature of the angular dependence (for substituent effects in allyl systems), as well as the extent to which the proportionality constant, k, might vary. Such knowledge would establish the reliability of the $\cos^2 \phi$ relation as a method of conformational analysis of the C(sp^2)–C(sp^3) bond in allyl groups.

Table II. Correlations of ^2J with Substituent Parameters

Substituent parameter	ρ^a	r^a	s^a	n^b
$\sigma_p{}^c$	2.9	0.823	0.632	8
$\mathcal{F} + \mathcal{R}^d$	18.0	0.710	0.816	7
$0.105\mathcal{F} + \mathcal{R}^d$	4.3	0.906	0.492	7
$0.1\mathcal{F} + \mathcal{R}^d$	3.7	0.903	0.497	7
$\delta_v{}^e$	1.13	0.962	0.307	9

[a] ρ represents the slope of the plot of ^2J *vs.* the specific parameter indicated, r is the correlation coefficient, and s is the standard deviation as derived from a least-squares analysis of the data.[24] [b] n is the number of compounds used in the plot. [c] σ_p values are taken from the compilation of D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958), except for the $CONH_2$ group whose σ_p is reported by M. Charton, *ibid.*, **28**, 3121 (1963). The morpholino group was not included, since no σ_p value is available. [d] $\mathcal{F}$ and $\mathcal{R}$ are the substituent parameters of Swain and Lupton.[26] Values are not available for the $-CONH_2$ or morpholino groups. [e] δ_v represents the chemical shifts of the vinyl protons at C-3 in series **2**.

Experimental Section

All boiling and melting points are uncorrected. The nmr spectra were recorded on a Varian HA-100 spectrometer equipped with an Nmr Specialties SD-100 spin decoupler operating at 15.3 MHz. All spectra, unless otherwise noted, were measured using 0.1 *M* solutions in deuteriochloroform and the chemical shifts are reported on the δ scale (ppm downfield from internal TMS). The values for the coupling constants reported herein are the average of at least 12 measurements. The standard deviations for the geminal coupling constants were all 0.1 Hz or less and for the long-range coupling constants 0.07 Hz or less. Chemical shifts are estimated to be accurate to 0.15 Hz. The ir spectra of solids were taken as KBr dispersions, those of liquids as neat films, both using a Beckman IR-20 spectrometer. The absorption frequencies are reported in units of cm^{-1}. Mass spectral analyses were performed using a Hitachi Perkin-Elmer RMU-6D spectrometer. Microanalyses were carried out by the Scandinavian Mikroanalytical Laboratory, Herlev, Denmark. Work-up is used to specify drying of extracts over magnesium sulfate, filtration, and concentration of the filtrate *in vacuo*.

Methyl 1-Methyl-4-oxocyclohexanecarboxylate (4). The method of Bruson and Reiner[29] was used to prepare γ-methyl-γ-carboxypimelic acid which was then converted to methyl 1-methyl-4-oxocyclohexanecarboxylate (**4**) by the procedure of Rubin and Wishinsky.[10] The product was purified by distillation, bp 53–57° (0.08 mm) [lit.[10] bp 80–83° (0.2 mm)].

Methyl 1-Methyl-4-methoxy-3-cyclohexenecarboxylate (2a). A solution of 284 mg (1.7 mmol) of **4** in 20 ml of anhydrous methanol was treated with 2 ml of glacial acetic acid. After standing overnight at room temperature, the mixture was added dropwise to a

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[27] It should be pointed out that the anisotropy of each X substituent will affect δ_v but not J. If one were able to allow for this contribution to δ_v, the correlation would doubtless be improved.

[28] U. E. Matter, C. Pascual, E. Pretsch, A. Pross, W. Simon, and S. Sternhell, *Tetrahedron*, **25**, 691, 2023 (1969). A similar survey of olefinic proton shifts is described by S. W. Tobey, *J. Org. Chem.*, **34**, 1281 (1969).

[29] H. A. Bruson and T. W. Reiner, *J. Amer. Chem. Soc.*, **64**, 2850 (1942).

rapidly stirred solution of sodium bicarbonate. The aqueous solution was extracted with chloroform. After work-up the residue was chromatographed on alumina (activity I) using cyclohexane–ethyl acetate (9:1) as eluent. Bult-to-bulb distillation of the material first eluted gave 268 mg (77%) of ketal: bp 45–50° (0.08 mm); ir 1715 (C=O); nmr 3.68 (s, 3 H), 3.16 (s) and 3.14 (s, total of 6 H), 2.3–1.3 (m, 6 H), 1.17 (s, 3 H).

Following the procedure of Eppenberger,[30] *et al.*, a solution of 200 mg (0.92 mmol) of this ketal in 1 ml of pyridine (previously dried over NaOH) was treated with 0.18 ml of phosphorus oxychloride. The mixture was refluxed for 2 hr. The temperature was then raised to 140–150° whereupon the volatile components were distilled off. After cooling, the dark-colored residue was added dropwise to a solution of sodium bicarbonate. After extraction with chloroform and work-up, the residue was chromatographed on alumina (activity 1) using cyclohexane–ethyl acetate (9:1) as eluent. Bulb-to-bulb distillation gave 110 mg (65%) of **2a**: bp 80–85° (5 mm); ir 1715 (C=O), 1655 (C=C); nmr 4.51 (m, 1 H), 3.65 (s, 3 H), 3.47 (s, 3 H), 2.8–1.4 (m, 6 H), 1.2 (s, 3 H); mass spectrum, *m/e* 184.

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.25; H, 8.69. Found: C, 65.07; H, 8.70.

Methyl 1-Methyl-4-(1′-morpholino)-3-cyclohexenecarboxylate (2b). A solution of 300 mg (1.7 mmol) of **4** in 20 ml of benzene was treated with a tenfold excess of morpholine. To this was added a catalytic amount of *p*-toluenesulfonic acid. The mixture was refluxed for 8 hr in a Soxhlet extractor containing calcium carbide. The solvents were removed under vacuum, and the residue was distilled (bulb-to-bulb) to give a 70–80% yield of **2b**, bp 85–90° (0.08 mm). The pmr spectrum of this liquid indicated the presence of a small amount of unreacted ketone which could not be eliminated despite several attempts to do so. This product hydrolyzes rapidly on exposure to air. For these reasons analysis was not attempted. The product showed ir 1720 (C=O), 1638 (C=C); nmr 4.58 (m, 1 H), 3.70 (t) and 3.66 (s, total of 7 H), 2.76 (t) and 2.8–1.4 (m, total of 10 H), 1.19 (s, 3 H); mass spectrum, *m/e* 239.

Methyl 1-Methyl-4-acetoxy-3-cyclohexenecarboxylate (2c). Following the procedure of Barton,[31] a mixture of 1.8 g (11 mmol) of **4**, 60 ml of carbon tetrachloride, 8.5 ml of acetic anhydride, and 5 drops of perchloric acid (70%) was stirred at room temperature for 3.5 hr. The resulting dark-colored solution was treated with decolorizing carbon and filtered and the solvent removed under vacuum. The crude product was chromatographed on silica using cyclohexane–ethyl acetate (7:3) as eluent. Bulb-to-bulb distillation gave 1.7 g (73%) of **2c**: bp 63–65° (0.06 mm); ir 1748 (acetate C=O), 1725 (ester C=O), 1690 (C=C); nmr 5.27 (m, 1 H), 3.67 (s, 3 H), 2.09 (s) and 2.9–1.4 (m, total of 9 H), 1.25 (s, 3 H); mass spectrum, *m/e* 212.

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.24; H, 7.59. Found: C, 62.26; H, 7.63.

Methyl 1-Methyl-4-chloro-3-cyclohexenecarboxylate (2d). Treatment of 2.6 g (15 mmol) of **4** with 3.3 g (16 mmol) of phosphorus pentachloride according to the procedure of Braude and Coles[32] gave the desired vinyl chloride along with a compound tentatively identified by mass spectral analysis as methyl 1-methyl-4,4′-dichlorocyclohexanecarboxylate. These compounds were not separable by distillation or by chromatography on silica.

The mixture was then treated with sodium methoxide in dimethyl sulfoxide at 40–50° for approximately 3 hr, poured into dilute acid, and extracted several times with pentane. After work-up, the residue was chromatographed on silica using cyclohexane–ethyl acetate (7:3) as eluent. Bulb-to-bulb distillation gave 0.8 g (27%) of **2d**: bp 33–35° (0.06 mm); ir 1720 (C=O), 1648 (C=C); nmr 5.72 (m, 1 H), 3.67 (s, 3 H), 2.9–1.4 (m, 6 H), 1.21 (s, 3 H); mass spectrum, *m/e* 188, 190.

Anal. Calcd for $C_9H_{13}O_2Cl$: C, 57.30; H, 6.95; Cl, 18.79. Found: C, 57.60; H, 6.97; Cl, 19.01.

Methyl 1-Methyl-3-cyclohexenecarboxylate (2e). This compound was prepared in two ways: (A) by reduction of the carbonyl group in **4** followed by tosylation and elimination reactions, and (B) by a Diels–Alder reaction between methyl methacrylate and butadiene sulfone.

Method A. A solution of 800 mg (4.7 mmol) of **4** in 10 ml of dry methanol was reduced using 500 mg of sodium borohydride. The mixture was stirred for 2 hr at 10–15°, poured into dilute hydrochloric acid, and extracted with chloroform. After work-up, the residue was chromatographed on silica using cyclohexene–ethyl acetate (7:3) as eluent. Prior to elution of the alcohol 75 mg of unreacted ketone was recovered. Bulb-to-bulb distillation of the major fraction gave 580 mg (79% based on reacted ketone) of methyl 1-methyl-4-hydroxycyclohexanecarboxylate: bp 68–73° (0.06 mm); ir 3400 (br OH), 1720 (br C=O); nmr 3.64 (s) and 3.6 (m, total of 4 H), 2.5–1.2 (m, 9 H), 1.16 (s) and 1.14 (s, total of 3 H).

A solution of 570 mg (0.33 mmol) of this alcohol in 10 ml of pyridine (dried over sodium hydroxide) was treated with 1.3 g of *p*-toluenesulfonyl chloride. After standing for 5 days at −20° the mixture was added dropwise to 40–50 g of an ice-water mixture. The product, which oiled out at first, gradually solidified and was filtered off, washed several times with water, and dried under vacuum. After two recrystallizations from petroleum ether (bp 30–60°), the product with mp 83–87° amounted to 945 mg (88% yield): ir 1720 (C=O), 1345, 1170 (S=O); nmr 7.8 (d, 2 H), 7.1 (d, 2 H), 4.5 (m, 1 H), 3.64 (s, 3 H), 2.41 (s) and 2.4–1.2 (m, total of 11 H), 1.04 (s) and 1.01 (s, total of 3 H).

A solution of 700 mg (2.2 mmol) of the above solid in 20 ml of 0.5 *M* potassium *tert*-butoxide was refluxed for 2 hr. After adding 5 ml of water, refluxing was continued for an additional 0.5 hr. After cooling, the basic solution was extracted once with chloroform, acidified, and extracted again with chloroform. The residue after work-up was esterified using silver oxide–methyl iodide. Chromatography of the product on silica using cyclohexane–ethyl acetate (9.5:0.5) as eluent gave **2e** in 25% yield.

Method B. A mixture of 1.0 g (8.5 mmol) of butadiene sulfone, 10 ml of dry toluene, 4.3 g of methyl methacrylate, and a few milligrams of hydroquinone was placed in a sealed tube and heated at 130° for 30 hr. After cooling, the solvents were removed under vacuum and the residue passed through 20 g of silica using cyclohexane–ethyl acetate (3:2) as eluent. The polymethyl methacrylate formed during the reaction remained on the column. Bulb-to-bulb distillation gave 770 mg (59%) of **2e**, bp 53–55° (5 mm). An analytical sample was prepared by an additional chromatography on silica using cyclohexane–ethyl acetate (8.5:1.5) as eluent prior to distillation. The distillate showed ir 1725 (C=O), 1645 (C=C); nmr 5.62 (m, 2 H), 3.75 (s, 3 H), 2.6–1.3 (m, 6 H), 1.3 (s, 3 H); mass spectrum *m/e* 154.

Anal. Calcd for $C_9H_{14}O_2$: C, 70.12; H, 9.15. Found: C, 70.06; H, 9.17.

Methyl 1-Methyl-4-phenyl-3-cyclohexenecarboxylate (2f). A solution of 1.2 g (7.7 mmol) of the acid[10] derived from **4** in 100 ml of anhydrous ether was placed in a 250-ml, three-neck flask equipped with a nitrogen inlet, a condenser protected from the atmosphere by a drying tube, and a serum cap. A solution of phenylmagnesium bromide, prepared from 2.6 g (16 mmol) of bromobenzene in 25 ml of anhydrous ether containing 0.4 g (16 g-atoms) of magnesium turnings, was added dropwise with a hypodermic syringe. After 8 hr of heating under reflux, the solution was cooled, dilute sulfuric acid added, and the ether layer separated. The aqueous layer was extracted with ether. The combined ether solutions were washed with base and the aqueous washings acidified and extracted with ether. The dried ether solution was treated with an ethereal solution of diazomethane. After 4 hr the solution was concentrated and the residue distilled to give 440 mg (23%) of methyl 1-methyl-4-hydroxy-4-phenylcyclohexanecarboxylate: bp 96–105° (0.05 mm); ir 3500 (OH), 1725, 1710 (ester C=O's), 755, 698 (phenyl); nmr 7.4 (m, 5 H), 3.69 (s, 3 H), 2.4–1.4 (m, 9 H), 1.25 (s) and 1.23 (s, total of 3 H). The doubling of C=O absorption in the ir and CH_3 peaks in the nmr indicates a mixture of cis–trans isomers.

Dehydration of 230 mg (0.93 mmol) of this alcohol mixture by treatment with 0.25 ml of $POCl_3$ in 4 ml of pyridine[33] gave a product which after chromatographic purification (silica, cyclohexane–ethyl acetate, 7:3, as eluent) was distilled, bulb-to-bulb. The distillate, bp 76–80° (0.06 mm), amounted to 151 mg (74% yield): ir 1726 (C=O), 1640 (C=C), 755, 692 (phenyl); nmr 7.3 (m, 5 H), 6.06 (m, 1 H), 3.67 (s, 3 H), 3.1–1.5 (m, 6 H), 1.25 (s, 3 H); mass spectrum, *m/e* 230.

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.22; H, 7.89. Found: C, 78.30; H, 7.93.

Methyl 1-Methyl-4-cyano-3-cyclohexenecarboxylate (2i). A solution of 2.0 g (12 mmol) of **4** and 2.3 g of potassium cyanide in 30

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[30] U. Eppenberger, M. E. Warren, and H. Rapoport, *Helv. Chim. Acta*, **51**, 381 (1968).

[31] D. H. R. Barton, D. A. J. Ives, and B. R. Thomas, *J. Chem. Soc.*, 903 (1954).

[32] E. A. Braude and J. A. Coles, *ibid.*, 2017 (1950).

[33] L. H. Sarrett, *J. Amer. Chem. Soc.*, **70**, 1454 (1948).

ml of dry methanol was stirred and maintained at 0° while 14 ml of glacial acetic acid was added dropwise over 20 min. After standing for 2 hr the solution was poured into water containing an excess of sodium bicarbonate and the water extracted with ether. Work-up followed by distillation gave 1.9 g (80%) of methyl 1-methyl-4-hydroxy-4-cyanocyclohexanecarboxylate: bp 90–96° (0.08 mm); ir 3430 (OH), 2220 (CN), 1725, 1708 (C═O); nmr 3.69 (s, 3 H), 3.2–1.5 (m, 9 H), 1.21 (s) and 1.19 (s, total of 3H) (a mixture of cis and trans isomers).

Dehydration of 1.1 g (5.6 mmol) of the cyanohydrin in the usual fashion[33] gave 750 mg (75%) of **2i**: bp 53–55° (0.08 mm); ir 2200 (CN), 1722 (C═O), 1635 (C═C); nmr 6.56 (m, 1 H), 3.69 (s, 3 H), 2.9–1.4 (m, 6 H), 1.22 (s, 3 H); mass spectrum, *m/e* 179.

Anal. Calcd for $C_{10}H_{13}O_2N$: C, 67.04; H, 7.31; N, 7.81. Found: C, 67.09; H, 7.31; N, 7.80.

Methyl 1-Methyl-4-carboxamido-3-cyclohexenecarboxylate (2g). A mixture of 165 mg (0.92 mmol) of **2i** in 10 ml of 1 *N* sodium hydroxide containing 15 ml of 30% hydrogen peroxide (w/v) was stirred at 30° for 10 min. The alkaline solution was extracted with chloroform. Work-up gave a white solid which after two recrystallizations from carbon tetrachloride weighed 78 mg (43%) and melted at 120–121°: ir 3365, 3160 (N–H), 1710 (ester C═O), 1665 (amide C═O), 1638 (C═C), 1600 (NH); nmr 6.58 (m, 1 H), 5.5 (br s, 2 H), 3.66 (s, 3 H), 3.0–1.4 (m, 6 H), 1.22 (s, 3 H); mass spectrum, *m/e* 197.

Anal. Calcd for $C_{10}H_{15}O_3N$: C, 60.87; H, 7.69; N, 7.11. Found: C, 60.95; H, 7.63; N, 7.10.

Dimethyl 1-Methyl-3-cyclohexene-1,4-dicarboxylate (2h). Basic hydrolysis of 550 mg (3 mmol) of **2g** with 1 *N* sodium hydroxide gave, after acidification of the solution, filtration, and recrystallization of the solid from acetone, 420 mg (76%) of solid: mp 247–249°; ir 3500–3200 (br OH), 1670 (br C═O), 1640 (C═C); nmr (trifluoroacetic acid) 7.32 (m, 1 H), 3.2–2.6 (m, 6 H), 1.36 (s, 3 H). A mixture of 300 mg of this solid and 1.6 g of silver oxide in 30 ml of 1,2-dimethoxyethane was heated to 45–50°. Excess methyl iodide was added, and stirring and heating were continued for 3 hr. The reaction mixture was filtered, and the filtrate concentrated. Chromatography of the residue on silica, using cyclohexane-ethyl acetate (4:1) as eluent, followed by distillation gave 280 mg (83%) of **2h**: bp 61–63° (0.06 mm); ir 1712 (C═O), 1640 (C═C); nmr 6.92 (m, 1 H), 3.71 (s, 3 H), 3.66 (s, 3 H), 2.9–1.4 (m, 6 H), 1.21 (s, 3 H); mass spectrum, *m/e* 212.

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.24; H, 7.59. Found: C, 62.19; H, 7.62.

Methyl 1-Methyl-3,3,5,5-tetradeuterio-4-oxocyclohexanecarboxylate (3). The ethyl ester[10] of 1-methyl-4-oxocyclohexanecarboxylic acid, 4.5 g (24 mmol), was hydrolyzed by heating in 100 ml of D_2O (99.5% D) containing NaOD formed by addition of 4 g of sodium. Work-up gave 3.0 g (78%) of solid which after recrystallization from benzene-petroleum ether had mp 77.5–79° (lit.[10] mp 78–79°). The deuterium content of this product was shown to be greater than 95 mol % d_4 by mass spectroscopic analysis. Esterification using methyl iodide and silver oxide gave methyl 1-methyl-3,3,5,5-tetradeuterio-4-oxocyclohexanecarboxylate in 90% yield.

Synthesis of Series 1, the 3,5,5-Trideuterio Derivatives of 2. The conversions of **3** to all members of series **1** were conducted as described above for the conversions **4** to **2**. The only changes made were to substitute deuteriums for any exchangeable protons in those reagents which might have promoted exchange of the deuteriums already present. For example acetic acid-*O-d*, methanol-*O-d*, and morpholine-*N-d* were utilized wherever necessary. The deuterium content of the final products **1a–i** were determined by low voltage mass spectral analysis.

The morpholino and acetoxy derivatives **1b** and **1c** were found to have greater than 85% incorporation of three deuterium atoms and the remaining seven members of series **1** all had greater than 95% incorporation of deuterium at positions 3 and 5.

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Stereochemistry of Asymmetric Silicon. XIX. Nucleophilic Substitutions Involving Hydrogen and Carbon as Leaving Groups and Further Demonstration of Stereochemistry Crossover[1–3]

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Abstract: In this paper it is demonstrated that the stereochemistry of nucleophilic replacement of hydrogen and carbon leaving groups from silicon is a sensitive function of the nature of the reagent, the solvent, and, for carbon as a leaving group, the nature of the leaving organic group. Reagents used are all strong nucleophiles.

Although preliminary treatment of a portion of the present work on R_3Si^*H has appeared,[4,5] the data on carbon as a leaving group are completely new and the older work on the reactions of R_3Si^*H with bases is useful for completeness and for demonstrating stereochemistry crossover by comparison with new work never published.

The silicon–hydrogen bond is certainly extremely important from both synthetic and mechanistic standpoints and the latter aspect can receive much clarification by stereochemical studies such as those reported herein. We shall demonstrate a certain sensitivity of stereochemistry to various factors which make it reasonably certain that SN2*-Si and SN2**-Si are not common mechanisms for the silicon–hydrogen bond in R_3Si^*H (R_3Si^* is α-naphthylphenylmethylsilyl).[6]

Perhaps the simplest reaction of R_3Si^*H with a nucleophile is H–D exchange with lithium aluminum deuteride

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(1) For the preceding paper in this series, see L. H. Sommer and D. L. Bauman, *J. Amer. Chem. Soc.*, **91**, 7076 (1969).

(2) In its initial stages, this work was done at the Pennsylvania State University with generous support by Dow Corning Corp.

(3) We thank the National Science Foundation for vital recent support.

(4) For a preliminary communication on isotopic H–D exchange at R_3Si^* with $LiAlH_4$, see L. H. Sommer and C. L. Frye, *J. Amer. Chem. Soc.*, **81**, 1013 (1959).

(5) For preliminary treatment of the nucleophilic displacements on R_3Si^*H with KOH and with *tert*-butoxide anion in *tert*-butyl alcohol solvent, see L. H. Sommer, "Stereochemistry, Mechanism and Silicon," McGraw-Hill, New York, N. Y., 1965, pp 104–106.

(6) For a summary of the meaning of the mechanism symbols used in this paper, see ref 5, Chapter 11.