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CONFIGURATIONAL AND CONFORMATIONAL ANALYSIS

AXIAL-AXIAL AND AXIAL-EQUATORIAL COUPLING CONSTANTS IN SIX-MEMBERED RING COMPOUNDS

A. C. HUITRIC, J. B. CARR,[1] W. F. TRAGER[2] and B. J. NIST
College of Pharmacy and Department of Chemistry, University of Washington

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Abstract—Axial-axial and axial-equatorial coupling constants (J_{aa} and J_{ae}) have been obtained directly from the NMR spectra of simple AB systems in a number of *cis*- and *trans*-1-(substituted)-2-arylcyclohexanes-3,3,6,6-d_4 measured in several solvents. Variations in J_{aa} and J_{ae} have been observed with various substituents. No simple correlation is found between electronegativity of substituents and substituent effects on coupling constants. A review of J_{aa} and J_{ae} in six-membered ring compounds is given.

DIHEDRAL angle dependency of coupling constants between protons on adjacent carbon atoms makes PMR the most powerful single tool now available for configurational and conformational analysis of substituted six-membered ring compounds. It is now well recognized, however, that in addition to angle dependency of coupling constants there exists superimposed substituent effects which are difficult to predict. Fortunately these effects are not significant enough to interfere in the differentiation between axial-axial and axial-equatorial orientation. In the investigation of substituent effects on coupling constants much attention has been given to the electronegativity of substituents. Although many authors report linear decrease of J_{HH} with increase in electronegativity of substituents the results of such correlations have not produced consistent results. A serious difficulty in such correlations involves the availability of meaningful electronegativity values for functional groups of more than one atom. The electronegativity values of Cavanaugh and Dailey[3] for polyatomic functional groups, used by Williamson,[4] are undoubtedly complicated by magnetic anisotropy factors. It is interesting to note that no simple correlation is found[5] between geminal J_{HH} and the electronegativity values of the halogens in CH_2DX, where X is F, Cl, Br or I, although the relative electronegativity values of the halogens are among the most reliable. Through valence bond treatment of substituent effects, Gutowsky and Juan[6] have correlated $J_{^{13}CH}$ with the *s* character of the carbon hybrid orbital of the C—H bond. There is little doubt that some relationship exists between substituent effects on J_{CH} and on J_{HH} in H—C—C—X fragments, and it therefore

[1] Fellow of the American Foundation for Pharmaceutical Education, 1961–63; Robert Lincoln McNeil Citation Fellow, 1962–63.
[2] Public Health Service Predoctoral Fellow, 1962–63.
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seems very improbable that any simple direct correlation should be expected between electronegativity of substituents and their effects on J_{HH} in such fragments, since no such simple correlation is found for J_{CH}.

Although substituent effects on J_{HH} are usually not significant enough to interfere in the differentiation between axial-axial and axial-equatorial or equatorial-equatorial orientation of hydrogens on adjacent carbons they undoubtedly contribute to the considerable variations in reported axial-axial coupling constants (J_{aa}) and axial-equatorial coupling constants (J_{ae}). Reported values for J_{ae} range from 2 to 7 c.p.s. and values for J_{aa} from 5 to 13·4 c.p.s.[7–29] Values of 3–4 c.p.s.[7,8] and 2·72 c.p.s.[16] have been reported for J_{ee}. The theoretical treatment of Karplus[30] predicts 9·2 and 1·72 c.p.s. for J_{aa} and J_{ae} respectively. Gutowsky and Juan[6] have observed J_{HH} of 12·3 c.p.s. for the adjacent *trans* hydrogens in (2, 2) metacyclophane (a molecule of fixed conformation), but J_{HH} values of 3·2 and 4·0 c.p.s. were observed for the gauche hydrogens, indicating that the *trans* dihedral angle is not exactly 180°.

Values reported from our own laboratories for substituted cyclohexanes have centered around 11·5 c.p.s. for J_{aa} and 3·5–4 c.p.s. for J_{ae}.[13,17,18,21,28] Since we have not always reported values for individual compounds[17,21] this is now done in Table 2. Table 1 lists values reported from other laboratories. The low values for the carbocyclic compounds listed in Ref. 8 have been shown to be in error.[11] It is of interest to note that most of the other low values in Table 1 were obtained from the signal of the proton on the anomeric carbon in heterocyclic compounds,[8,20,25]

Coupling constants listed in Table 2 were obtained directly from the spectra by simple first order treatment. With the exceptions of the *trans* nitro compounds the values were obtained from the signal of the proton on C-2 of *cis*-2-aryl-1-substituted

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TABLE 1. AXIAL-AXIAL AND AXIAL-EQUATORIAL COUPLING CONSTANTS IN SIX-MEMBERED RING COMPOUNDS[a]

Compounds	J_{aa} c.p.s.	J_{ae} c.p.s.	References
1α, 3α-Dimethoxy-2β-acetoxycyclohexane	9		7, 8
1α, 3β-Dimethoxy-2α-acetoxycyclohexane	6·4	2·6	8
A series of acetylated aldopyranoses	5–8[b]	2–3·2[b]	8
A series of saccharides	6·2–8·8[b]	2·3–3·8[b]	25
Allo-Quercitol	9	3	14
Actinamine	9	3	23
Talo-Quercitol	10	2	12
Phenyldecalones	10	4	26
Dioxane	9·4[c]	2·7[c]	9
6-Methyl-3-piperidinol	9·2	4·4	24
Trans-3,3,4,5,5,-Pentadeuterio-4-*t*-butylcyclohexanol	11·07	4·31	16
3,3,4,4,5,5-Hexadeuteriocyclohexyl acetate	11·43	4·24	16
Desosamine	7·8[b] 10·2 12·0 11·1	3·9 1·8 4·0	20
Diacetyldesosamine hydrochloride	7·6[b] 10·4 12·5 11·1	4·2 1·9	20
6α-Hydroxy-17-ethylenedioxy-3α	12[d]	4·3[d]	22
5α-cycloandrostane	11·5[e]	4·4[e]	
1,1,4,4-Tetramethylcyclohexyl *cis*-2,6-diacetate	12·35	4·25	10
A series of cholestanes, cholestane-3-ones and 2-ones	9·5–13·1	2·5–7·4	15
A series of deuterated cholestane-3-ones		6·4–7·0	19
A series of 2-Bromo-3-oxo-steroids	12·4–13·4	5·7–8	27
Phthalimidocyclohexane and its *trans* 2-ethyl derivative	11·4 11·6	3·8 3·95	29

[a] Values obtained from the literature.
[b] Values obtained from the signal of the proton on the anomeric carbon atom.
[c] Obtained from ^{13}C satallites.
[d] Values from the acetate.
[e] Values from the *p*-nitrobenzoate.

cyclohexanes. The constancy of J_{aa} in these compounds is not unexpected even with a variation of the substituent on C-1 (providing no distortion of bond angle results), because the coupling constants were obtained from essentially the same AR—C(H)—C(H)— fragment between protons on C-2 and C-3.

Current work in our laboratories has required the synthesis of certain *trans*-2-arylnitrocyclohexanes-3,3,6,6,-d_4. These compounds serve as ideal intermediates for the preparation of several 1,2-disubstituted cyclohexanes giving simple AB systems from which J_{aa} and J_{ae} can be obtained unambiguously from first-order spectra, and from which substituent effects on coupling constants can be observed. Such compounds have been prepared and the pertinent NMR data is given in Tables 3 and 4. In the

trans series (Table 3), with the exception of the trifluoroacetate salts of VIII and IX in trifluoroacetic acid, the signals of H-1 and H-2 were both clean doublets in which the peaks showed slight broadening due to coupling with adjacent deuterium atoms. Deuterium decoupling on compound III and VII gave very sharp doublets with no change in coupling constants. The spectra of VIII and IX in trifluoroacetic acid give nice doublets for H-2 but the signals of H-1 are complicated by coupling with the

TABLE 2. AXIAL-AXIAL AND AXIAL-EQUATORIAL COUPLING CONSTANTS IN SUBSTITUTED CYCLOHEXANES[a]

Compounds	J_{aa}		J_{ae}		References
cis-2-*o*-Tolylcyclohexanol	11·8	11·5[b]			13
cis-2-(*o*-Chlorophenyl)-cyclohexanol	11·6	11·0[b]			17
cis-2-(*m*-Chlorophenyl)-cyclohexanol	11·6	11·1[b]			17
cis-2-(*p*-Chlorophenyl)-cyclohexanol	11·2	10·9[b]			17
2-*o*-Tolylnitrocyclohexane	11·8[c]	10·5[d]	3·8[c]	3·9[d]	21
2-*p*-Tolylnitrocyclohexane	12·1[c]	10·6[d]		4·2[d]	21
2-(*o*-Chlorophenyl)nitrocyclohexane	12·4[c]	10·9[d]		4·1[d]	21
2-(*m*-Chlorophenyl)nitrocyclohexane	12·2[c]	10·8[d]		3·9[d]	21
2-(*p*-Chlorophenyl)nitrocyclohexane	11·6[c]	10·7[d]		3·9[d]	21
cis-2-*p*-Tolylcyclohexylamine		11·6			21
cis-2-(*m*-Chlorophenyl)cyclohexylamine		11·6			21
cis-2-(*p*-Chlorophenyl)cyclohexylamine		11·8			21
1-Ethynyl-2-*o*-tolylcyclohexanol	11·5[e]	10·7[f]	3·4[e]	3·5[f]	28
1-Ethynyl-2-*m*-tolylcyclohexanol	11·6[e]	10·5[f]	3·7[e]	3·9[f]	28
1-Ethynyl-2-*p*-tolylcyclohexanol	11·5[e]	10·2[f]	3·6[e]	4·0[f]	28
1-Ethyl-*cis*-2-*o*-tolylcyclohexanol		11·2		3·5	28
trans-4-t-Butylnitrocyclohexane		11·3		4·2	18

[a] Values previously obtained in our laboratories. In the aromatic substituted compounds the values were obtained from the signal of the proton on C-2 unless otherwise specified.

[b] Values for the corresponding acetates.

[c] Values obtained from the spectra of the *cis* isomers.

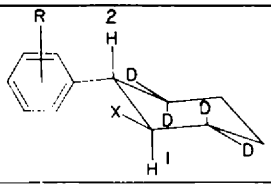
[d] Values obtained from the sextet of the proton on C-1 of *trans* isomers.

[e] Values for the *cis* isomers (OH axial).

[f] Values for the *trans* isomers (OH equatorial).

protons on the nitrogen, In the *cis* series (Table 4) every compound had at least one of the signals of the AB system appearing as a well-defined doublet from which J_{ae} could be obtained directly, but in certain compounds one of the signals was poorly resolved due to broadening resulting from coupling with adjacent deuterium atoms. The signals of both H-1 and H-2 were well-defined doublets for the hydrochloride salts of XV and XVI measured in D_2O. The signals of H-1 were well-defined doublets in the free amines XIII and XIV measured in tertachloroethylene, XIV measured in pyridine, the nitro compounds X and XI and the hydroxy compound XII, but in these compounds the signals of H-2 were poorly resolved, the complications being least for the nitro compounds. With the trifluoroacetate salts of XV and XVI in trifluoroacetic acid the signals of H-1 were complicated from coupling of H-1 with the protons on the nitrogen but the signals of H-2 appear as well-defined doublets. Deuterium decoupling on XI and XIV gave two very sharp doublets in each case with no change in coupling constants. The well-defined doublets for the

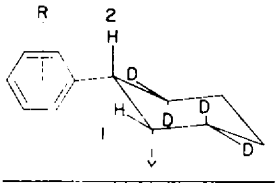
TABLE 3. AXIAL-AXIAL COUPLING CONSTANTS IN *trans*-2-ARYL-1-SUBSTITUTED CYCLOHEXANE-3,3,6,6-d_4



	Chemical shift, τ, ppm				J_{aa}, c.p.s.	
	X—C(H)—		AR—C(H)—		Solvent	
	CCl_4	Pyridine	CCl_4	Pyridine	CCl_4	Pyridine
I. X = D; R = *o*-CH_3			7·41	7·31	11·9	11·9
II. X = NO_2; R = *o*-CH_3	5·32		6·63		11·5	
III. X = NO_2 R = *p*-Cl	5·40		6·96		11·4 11·5[a]	
IV. X = OH R = *o*-CH_3	6·61	6·12	7·48	7·11	9·7	9·8
V. X = ϕ—C(=O)—O; R = *o*-CH_3	4·84		6·96		10·9	
	$Cl_2C=CCl_2$		$Cl_2C=CCl_2$			
VI. X = NH_2; R = *o*-CH_3	7·14	7·04	7·51	7·37	9·5	9·6
VII. X = NH_2; R = *p*-Cl	7·35	7·30	7·92	7·83	9·9 10·0[a]	
	D_2O $\ominus$ $\ominus$ $B=Cl$	F_3CCOOH	D_2O $\ominus$ $\ominus$ $B=Cl$	F_3CCOOH	D_2O $\ominus$ $\ominus$ $B=Cl$	F_3CCOOH
VIII. X = $\overset{\oplus\ominus}{N}H_3B$; R = *o*-$CH_3$	6·45	6·25	6·98	6·93	10·9	11·1
IX. X = $\overset{\oplus\ominus}{N}H_3B$; R = *p*-Cl	b	6·5		7·3		11·1

[a] Deuterium decoupled. [b] Insufficient solubility in D_2O.

TABLE 4. AXIAL-EQUATORIAL COUPLING CONSTANTS IN *cis*-2-ARYL-1-SUBSTITUTED CYCLOHEXANE-3,3,6,6-d_4



	Chemical shift, τ, ppm				J_{ae}, c.p.s.	
	H—C(X)—		AR—C(H)—		Solvent	
	CCl_4	Pyridine	CCl_4	Pyridine	CCl_4	Pyridine
X. X = NO_2; R = *o*-CH_3	5·30		6·93		3·7	
XI. X = NO_2; R = *p*-Cl	5·21		7·08		4·0 4·0[a]	
XII. X = OH; R = *o*-CH_3	6·32		7·21		1·9	
	$Cl_2C=CCl_2$		$Cl_2C=CCl_2$		$Cl_2C=CCl_2$	
XIII. X = NH_2; R = *o*-CH_3	6·87		7·09		2·6	
XIV. X = NH_2 R = *p*-Cl	6·89	6·80	7·40	7·32	2·8 3·0[a]	2·8
	D_2O $\ominus$ $\ominus$ $B=Cl$	F_3CCOOH	D_2O $\ominus$ $\ominus$ $B=Cl$	F_3CCOOH	D_2O $\ominus$ $\ominus$ $B=Cl$	F_3CCOOH
XV. X = $\overset{\oplus\ominus}{N}H_3B$; R = *o*-$CH_3$	6·31	6·12	6·68	6·58	3·2	2·9
XVI. X = $\overset{\ominus\ominus}{N}H_3B$; R = *p*-Cl	6·17	6·04	6·87	6·79	3·5	3·4

[a] Deuterium decoupled.

signals of H-1 in all free amines measured in tetrachloroethylene and their hydrochloride salts measured in D_2O show that the nitrogen protons are not coupled with H-1 in these compounds, indicating a rapid exchange of the nitrogen protons at the given conditions. The suppression of exchange in trifluoroacetic acid is as expected.

The results listed in Tables 3 and 4 show considerable substituent effects on coupling constants. These effects cannot be explained altogether on the basis of bond angle changes. Effects due to bond angle changes resulting from steric interactions would not be expected to be in the same direction for the *cis* and *trans* isomers of each diastereoisomeric pair. Substituent effects resulting from bond angle changes due to intramolecular hydrogen bonding of the OH or NH_2 groups with the π electrons of the aromatic ring in IV,VI,VII, XIII and XIV should be sensitive to solvent changes, but the coupling constants in IV, VI, VII and XIV were found to remain constant when the solvent was changed from carbon tetrachloride or tetrachloroethylene to pyridine. In pyridine the hydroxyl or amino groups are hydrogen bonded to the solvent. This is evident from the large downfield shift of the signal of the protons from these functional groups in pyridine. The constancy of the coupling constants of XIII, XV, and XVI when measured as the hydrochloride salt in D_2O or the trifluoacetate in trifluoroacetic acid indicates that bond angle changes are slight in these systems in the two different solvents.

It should be noted that the direction of substituent effects on coupling constants for compounds listed in Tables 3 and 4 is not one of general decrease of coupling constants with increase in electronegativity of substituents. The effect is actually in the opposite direction in going from the hydroxyl group to the benzoate and from the amino group to the ammonium cation. The nitro group is certainly more electronegative than a hydroxyl or an amino group, but the coupling constant are larger for the nitro compounds than for the corresponding alcohols or amines. The discrepancy of these results with results of authors who have found a linear decrease in J_{HH} with increase in electronegativity of substitutents cannot be reconciled on the basis of effects arising from bond angle changes in compounds listed in Tables 3 and 4. It should be noted that J_{aa} of compound I is in good agreement with the coupling constant between the *trans* protons in (2, 2) metacyclophane.[6]

The experimental results reported in this communication re-emphasize the power of NMR as a tool in configurational and conformational analysis, but they also demonstrate that caution must be exercised in looking for simple explanations for substituent effects on coupling constants. The results also re-emphasize the serious hazards involved in making calculations of bond angles from coupling constants.

Compounds II through XIV were prepared by methods previously described for the preparation of the corresponding hydrogen containing compounds.[17,21] The synthetic scheme involves a Diels–Alder condensation of butadiene with the appropriate *trans*-β-nitrostyrene to give the *trans*-4-nitro-5-arylcyclohexene. Hydrogenation of the double bond gives the corresponding *trans*-2-arylnitrocyclohexane, which can be isomerized to the *cis* isomer. Reduction of the nitro compounds gives the corresponding amines. The selective incorporation of deuterium on carbons 3 and 6 of compounds I through XVI was accomplished by using butadiene-1,1,4,4-d_4[31] instead of butadiene in the Diels–Alder condensation step of the synthetic scheme. The alcohols

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IV and XII were obtained from *trans*-4-nitro-5-*o*-tolylcyclohexene-3,3,6,6-d_4 by converting this compound to the corresponding ketone by a Nef reaction, followed by lithium aluminum hydride reduction of the ketone and subsequent hydrogenation of the double bond. The mixture of *trans* and *cis* alcohols IV and XII were separated by elution chromatography on alumina. The hydrogen containing compounds corresponding to compounds II, VI, VII, VIII, IX, X, XI, XIII, XIV XV and XVI have been reported in reference 21, those corresponding to IV and XII have been reported in reference 13, and that corresponding to III has been reported in reference 17. Compound I was prepared by reacting the tosylate of XII with lithium aluminum deuteride. A certain amount of elimination product also resulted from this reaction, as is evident from the NMR signal of a vinylic proton at 4·7$_\tau$. The signals of the elimination product did not interfere in any way with the doublet of H-2 of compound I and the components were not separated.

The spectra were determined with an HR-60 Varian spectrometer as solutions of about 20% in the solvents listed in Tables 3 and 4. The chemical shifts, expressed as *tau* units, are referred to tetramethylsilane used as internal reference for solutions in carbon tetrachloride, tetrachloroethylene, pyridine and trifluoroacetic acid, and to the $(CH_3)_3Si$- signal of sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) for solutions in deuterium oxide. Calibration was done by the side band method. Repeated runs gave a probable error of $\pm 0{\cdot}2$ cycles for coupling constants reported in Tables 3 and 4.

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