[CONTRIBUTION FROM THE RESEARCH LABORATORIES, SYNTEX, S. A., MEXICO, D. F., MEXICO]

Steroids. CCLXII.[1a] Spectra and Stereochemistry. XVI.[1b] A Study of the Mechanism of Long-Range 19-Proton–6β-Fluorine Coupling in 6β-Fluorosteroids

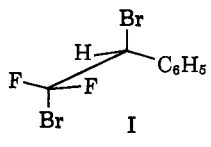
BY ALEXANDER D. CROSS

RECEIVED APRIL 27, 1964

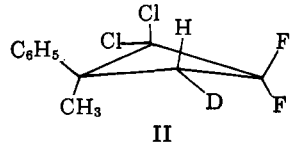
Nuclear magnetic resonance (n.m.r.) spectral data for numerous 6β-fluorosteroids are analyzed. The effects of other substituents in the molecule on the magnitude of the 19-proton–6β-fluorine spin–spin coupling constants are studied in detail. Possible coupling mechanisms are discussed. Data for 6β- and 11β-fluorosteroids show that an electronegative substituent on the chain of bonds between the two coupling nuclei raises the value of the coupling constant. The available data suggest that increases or decreases of $J_{19H,6\beta F}$ associated with other substituent groups are additive.

Concurrent with the ever-increasing applications of n.m.r. spectroscopy to a broad range of physical and chemical problems there have appeared many reports of long-range spin–spin coupling of nuclei (coupling of nuclei more than three bonds apart). However, until recently, comparatively little attention has been concentrated on the geometrical requirements for long-range coupling through a saturated system of bonds. Strong proton–proton spin–spin coupling through four σ-bonds occurs in bicyclo[2.1.1]hexanes[2,3] and bicyclo[2.2.1]heptanes[4] for which the stereochemical relationship of the coupling protons was shown to be a critical factor. Further similar examples have been reported very recently.[5] Wiberg and his collaborators[3] found a great disparity between calculated and observed coupling constants for calculations based on overlap integrals and wave functions, and the assumption that the Fermi contact potential is the most important contributor to long-range spin–spin coupling.

In the less studied field of proton–fluorine coupling, Roberts and his school showed that only the *gauche* fluorine of the difluoro compound I couples with phenyl protons.[6] In an elegant study they demonstrated that



I

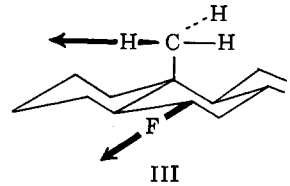


II

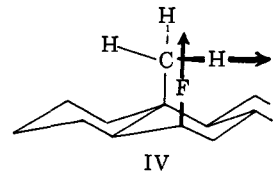
in the difluorinated cyclobutane II only that fluorine atom on the same side of the cyclobutane ring as the methyl couples through five σ-bonds with the methyl protons.[7] This conclusion was conditional upon there being no very unusual reversal of the relative magnitudes of the coupling constants of fluorine with the *cis* and *trans* protons of adjacent methylene. Almost simultaneous with these disclosures there was observed, independently, long-range spin–spin coupling of steroid angular methyl protons with fluorine substituted at various sites in the steroid nucleus.[8,9] Further studies of this phenomenon revealed that the coupling fluorine and proton necessary to maintain a limiting stereochemical relationship for coupling to occur between nuclei separated by five or more σ-bonds, and an assessment of this requirement culminated in the formulation of the empirical converging-vector rule.[10,11] A broad survey of extensive n.m.r. studies followed.[1b]

One interpretation of the converging-vector rule would be that transmission of spin-state knowledge between the coupling nuclei occurs through orbital overlap *across space*. The accumulated evidence[1b,9,10] at first sight appears strongly suggestive of that mechanism. Alternatively, the stereochemical requirements might be indicative of a need to maintain a highly favorable set of bond angles along the chain of bonds connecting the coupling nuclei, to permit transmission of spin-state knowledge through the intervening bonding electrons. To investigate the coupling mechanism a detailed study of readily-available 6β-fluorosteroids was undertaken. It appeared reasonable to suppose that other substituents, not necessarily present on the interconnecting C_{19}–C_{10}–C_5–C_6 chain of carbon–carbon bonds, might exercise marked effects upon the magnitude of the coupling constant $J_{19H,6\beta F}$ dependent upon the mechanism of the long-range proton–fluorine coupling. It was anticipated that for a through-space coupling mechanism any structural modification leading to an *increase* of the 19-proton–6β-fluorine distance, r, would be reflected in a *decrease* in the magnitude of the spin–spin coupling constant. Conversely, the effect of substituent groups on a through-bonding-electrons coupling mechanism might be expected to be more related to changes induced in the bond angles, and hence the extent of orbital overlap, along the chain of bonds between the coupling nuclei. Electronegative substituents on the connecting chain, or nearby, would lead to some rehybridization of orbitals, with concomitant change of bond angles, besides inducing positive charge at one or more carbons along the chain.

For 6-fluorosteroids the converging-vector rule[1b,10] predicts 19-H–F coupling for 6β- but not for 6α-fluorosteroids, as is illustrated in part structures III and IV.



III



IV

(1) (a) Steroids. CCLXI: P. Crabbé and C. Casas Campillo, manuscript in preparation; (b) Spectra and Stereochemistry. XV: A. D. Cross and P. W. Landis, *J. Am. Chem. Soc.*, **86**, 4005 (1964).

(2) J. Meinwald and A. Lewis, *ibid.*, **83**, 2769 (1961).

(3) K. B. Wiberg, B. R. Lowry, and B. J. Nist, *ibid.*, **84**, 1596 (1962).

(4) F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961); J. Meinwald and Y. C. Meinwald, *J. Am. Chem. Soc.*, **85**, 2514 (1963).

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

(6) D. R. Davis, J. P. Lutz, and J. D. Roberts, *J. Am. Chem. Soc.*, **83**, 246 (1961).

(7) M. Takahashi, D. R. Davis, and J. D. Roberts, *ibid.*, **84**, 2935 (1962).

(8) G. Slomp, private communication.

(9) A. D. Cross and P. W. Landis, *J. Am. Chem. Soc.*, **84**, 1736 (1962).

(10) A. D. Cross and P. W. Landis, *ibid.*, **84**, 3784 (1962).

(11) It is of distinct interest that the converging vector rule, though so far applied only to steroids, predicts the result which Roberts and coworkers arrived at.

TABLE I

CHEMICAL SHIFTS, ν, AND COUPLING CONSTANTS, $J_{19H.6\beta F}$, FOR ANGULAR METHYL PROTON RESONANCES OF 6β-FLUOROSTEROIDS[12]

	Compound	ν_{18}-H	ν_{19}-H	Ref.
V	6β-Fluoroandrostane-3β,5α,17β-triol 3β,17β-diacetate[a]	48.1	64.8, 69.3	b
			J_{HF} 4.5	
VI	6β-Fluoropregn-4-ene-3,20-dione	41[c]	77, 79[c]	7
			J_{HF} 2	
		43.2[c]	78[c]	d
		42.5[a]	77.7, 79.5[a]	b
			J_{HF} 1.8	
VII	5α-Bromo-6β-fluoro-3β-hydroxy-16α-methylpregnan-20-one[c]	39.8	72.6, 77.2	e
			J_{HF} 4.6	
VIII	3β,6β-Difluoro-5α,17α-dihydroxypregnan-20-one 17α-acetate[c]	38.6	65.4, 69.7	f
			J_{HF} 4.5	
IX	6β-Fluoro-3β,5α,17α-trihydroxypregnan-20-one 17α-acetate[a]	40.1	67.0, 71.7	g
			J_{HF} 4.7	
X	6β-Fluoro-5α,21-dihydroxypregnane-3,20-dione 3,20-bisethylene ketal[a]	48.7	64.1, 69.3	e
			J_{HF} 5.2	
XI	6β-Fluoro-3β,5α-dihydroxypregn-16-en-20-one 3β-acetate[c]	54.3	66.3, 70.6	e
			J_{HF} 4.3	
XII	3β,6β-Difluoro-17α-hydroxypregn-4-en-20-one acetate[h]	39.4	70.5, 72.4	8
			J_{HF} 1.9	
XIII	6β-Fluoro-5α-hydroxypregnane-3,20-dione 3-ethylene ketal[a]	38.0	61.5, 66.5	i
			J_{HF} 5	
XIV	5α-Bromo-6β-fluoro-3β-hydroxypregnan-20-one[c]	38.1	72.1, 76.9	k
			J_{HF} 4.8	
XV	6β-Fluoro-5α,11β,21-trihydroxypregn-17(20)-en-3-one 3-ethylene ketal 21-acetate	...	69.7, 76.7	l
			J_{HF} 7	
XVI	5α-Bromo-6β-fluoro-3β,21-dihydroxypregnan-20-one 21-acetate 16α,17α-epoxide[c]	65.5	72.4, 76.7	m
			J_{HF} 4.3	
XVII	6β-Fluoro-3β,5α,16α,17α,21-pentahydroxypregnan-20-one 21-acetate 16α,17α-acetonide[c]	38.4	63.2, 67.9	n
			J_{HF} 4.7	
XVIII	5α-Bromo-6β-fluoro-3β,16α,17α,21-tetrahydroxypregnan-20-one 3-acetate 16α,17α-acetonide[c]	36.0	75.5, 80.0	e
			J_{HF} 4.5	
XIX	5α-Bromo-6β-fluoro-3β,16α,17α,21-tetrahydroxypregnan-20-one 21-acetate 16α,17α-acetonide[c]	35.8	72.8, 77.6	e
			J_{HF} 4.8	
XX	5α-Bromo-6β-fluoro-3β,17α,21-trihydroxypregnan-20-one 17α,21-diacetate[a]	42.9	72.5, 76.5	k
			J_{HF} 4.0	
XXI	6β-Fluoro-3β,17α,21-trihydroxypregn-4-en-20-one triacetate[a]	45.5	71.0, 72.7	e
			J_{HF} 1.7	
XXII	6β-Fluoro-17α,21-dihydroxypregn-4-ene-3,20-dione diacetate[a]	47.8	78.2, 79.8	j
			J_{HF} 1.6	
XXIII	6β-Fluoro-3β,5α,17α,21-tetrahydroxypregnan-20-one 3β,17α,21-triacetate[a]	42.7	64.7, 69.2	e
			J_{HF} 4.5	
XXIV	6β-Fluoro-5α,17α,21-trihydroxypregnane-3,11,20-trione 3-ethylene ketal 17α,21-diacetate[c]	41.0	74.2, 78.4	o
			J_{HF} 4.2	
XXV	6β-Fluoro-5α-hydroxy-17α,20; 20,21-bismethylenedioxypregnane-3,11-dione 3-ethylene ketal[c]	47.0	72.7, 77.3	e
			J_{HF} 4.6	
XXVI	6β-Fluoro-5α,17α,21-trihydroxypregnane-3,11,20-trione 17α,21-diacetate[a]	44.4	88.8, 91.2	p
			J_{HF} *ca.* 2.5	
XXVII	5α-Bromo-6β-fluoro-3β-hydroxyandrostan-17-one acetate[c]	53.5	75.7, 80.2	e
			J_{HF} 4.5	
XXVIII	6β-Fluoro-17β-hydroxy-5α-androstan-3-one acetate[c]	51.0	70.0, 72.2	17
			J_{HF} 2.2	
XXIX	6β-Fluoro-3β,5α-dihydroxyandrostan-17-one 3β-acetate[a]	52.3	65.7, 70.2	q
			J_{HF} 4.5	
XXX	6β-Fluoro-5α-hydroxyandrostane-3,17-dione[a]	54.7	76.2, 79.9	b
			J_{HF} 3.7	

[a] Data for chloroform solution. [b] A. Bowers and H. J. Ringold, *Tetrahedron*, **3**, 14 (1958). [c] Data for deuteriochloroform solution. [d] K. Tori and K. Kuriyama, *Chem. Ind.* (London), 1525 (1963). [e] A. Bowers, unpublished results. [f] J. A. Edwards unpublished results. [g] A. Bowers, L. Cuéllar Ibáñez, and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 5991 (1959). [h] Data for carbon tetrachloride solution. [i] A. Bowers, L. Cuéllar Ibáñez, and H. J. Ringold, *Tetrahedron*, **7**, 138 (1959). [k] A. Bowers, *J. Am. Chem. Soc.*, **81**, 4107 (1959). [l] Data quoted in ref. 24. [m] J. S. Mills and A. Bowers, U. S. Patent 3,014,938. [n] J. S. Mills, A. Bowers, C. Djerassi, and H. J. Ringold, *J. Am. Chem. Soc.*, **82**, 3399 (1960). [o] A. Bowers, E. Denot, M. Blanca Sánchez, and H. J. Ringold, *Tetrahedron*, **7**, 153 (1959). [p] H. J. Ringold, A. Bowers, O. Mancera, and G. Rosenkranz, U. S. Patent 2,951,840. [q] L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, and A. D. Cross, *J. Org. Chem.*, **29**, 2187 (1964).

6α-Fluorosteroids have been discussed in detail earlier[1b]; n.m.r. data for 6β-fluorosteroids are collected in Table I.[12] Structural modifications are limited to six centers of the steroid nucleus. It was noticed that in no case is the 18-proton resonance other than a singlet, for reasons amply discussed elsewhere.[1b]

(12) N.m.r. spectra were taken in deuteriochloroform or chloroform except as indicated otherwise. Solutions contained a little tetramethylsilane (TMS) as an internal reference standard. Chemical shifts, ν, are quoted in c.p.s. units from the TMS reference (0.0 c.p.s.) and are accurate

TABLE II

VARIATION OF $J_{19H6,5\beta F}$[12] WITH STEROID STRUCTURE AND 6β-F–19-H DISTANCES, r[13]

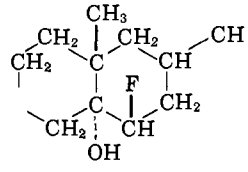
Section	Steroid	Substitution pattern C-3β	C-4	C-5α	C-11	$J_{19H,6\beta F}$, c.p.s.	r, Å.[13]
A	V	OAc	H_2	OH	H_2	4.5	1.61
	XI	OAc	H_2	OH	H_2	4.3	1.61
	XXIII	OAc	H_2	OH	H_2	4.5	1.61
	XXIX	OAc	H_2	OH	H_2	4.5	1.61
	XVIII	OAc	H_2	Br	H_2	4.5	1.61
	XXVII	OAc	H_2	Br	H_2	4.5	1.61
	VII	OH	H_2	Br	H_2	4.8	1.61
	XIV	OH	H_2	Br	H_2	4.8	1.61
	XVI	OH	H_2	Br	H_2	4.0	1.61
	XIX	OH	H_2	Br	H_2	4.6	1.61
	XX	OH	H_2	Br	H_2	4.3	1.61
	IX	OH	H_2	OH	H_2	4.7	1.61
	XVII	OH	H_2	OH	H_2	4.7	1.61
	XVIII	F	H_2	OH	H_2	4.2	1.61
B	X	Cy[a]	H_2	OH	H_2	5	1.61
	XIII	Cy[a]	H_2	OH	H_2	5.2	1.61
	XV	Cy[a]	H_2	OH	βOH	7	1.61
	XXIV	Cy[a]	H_2	OH	Ketone	4.2	1.58
	XXV	Cy[a]	H_2	OH	Ketone	4.6	1.58
C	XXX	Ketone	H_2	OH	H_2	3.7	1.59
D	XXVI	Ketone	H_2	OH	Ketone	*ca.* 2.5	1.60
E	XXVIII	Ketone	H_2	H	H_2	2.2	1.59
F	VI	Ketone	4,5 double bond		H_2	1.8	2.60
	XXII	Ketone	4,5 double bond		H_2	1.6	2.60
	XII	F	4,5 double bond		H_2	1.9	2.48
	XXI	OAc	4,5 double bond		H_2	1.7	2.48

[a] Cy = cycloethylene ketal.

From the collected data it is readily apparent that the nature of the substituents of ring D and the degree of hybridization of C-16 and C-17 exercise a negligible influence on the magnitude of $J_{19H,6\beta F}$. This point is illustrated by a comparison of steroids V, XI, and XXIX. Discussion hereafter is restricted therefore to the structural differences at carbon atoms 3-, 4-, 5-, and and 11-. In Table II values of $J_{19H,6\beta F}$ are shown in conjunction with structural variations at these four centers and distances, r, of the 6β-fluorine atom from the *nearest* possible 19-proton.[13] Choice of the distance to measure was made primarily on the assumption that if a through-space coupling mechanism is operative then the nearest 19-proton is expected to couple more strongly than more distant ones, orbital overlap being much greater for this orientation. A point relative to examination of the data is that except for a few Δ^4-steroids all the compounds studied have a five sp^3-hybridized carbon atom chain connecting the coupling nuclei. Table II is divided into sections each corresponding to certain structural features.

Section A of Table II comprises fourteen 6β-fluorosteroids in which structural variations, in rings A, B, and C, are at C-3 and C-5 only. Since both of these centers retain sp^3-hybridization of orbitals and no strong dipolar repulsions or steric interactions exist likely to promote ring distortion or bond angle deformation, a fairly constant value of $J_{19H,6\beta F}$ is expected for the range of structures studied. This is in fact observed. Both coupling mechanisms under consideration are compatible with this result. The distance r is essentially unchanged by substitution of hydroxyl for bromine at C-5. Comparison of sections A and F (Δ^4-steroids) at first sight seemingly lends support to the through-space coupling mechanism in that an increase of r from 1.61 to 2.48–2.60 Å. is accompanied by a sharp fall in $J_{19H6,\beta F}$ from *ca.* 4.5 to *ca.* 1.8 c.p.s. However, such a fall might equally well be interpreted as coupling through the electrons of the interconnecting chain of bonds since now C-5 is sp^2- rather than sp^3-hybridized. Coupling through several bonds does not involve just a single canonical form of the molecular structure. Rather, the observed coupling is a summation of the individual couplings operating for each possible canonical form which contributes to the structure. With an sp^2-hybridized carbon atom in the chain of bonds it might be that more of the individual couplings have an opposite sign, thus leading to an over-all smaller observed coupling for the molecule.

The data in sections A–D of Table II reveal some interesting correlations of structure and coupling constant magnitude. Except for seven 5α-bromo-6β-fluorosteroids in section A all the listed compounds have an identical structural unit (A) incorporating the coupling 6β-F and 19-H nuclei, with the structural constancy extending to a minimum of one carbon atom distant from any point along the chain. Structure variation is limited to C-3 and C-11 in rings, A, B, and C. The



A

19-H–F internuclear distance, r, varies only over the narrow range 1.58–1.61 Å. Nevertheless, in spite of these major consistencies there is a variation of $J_{19H,6\beta F}$ from *ca.* 2.5 to 7 c.p.s. From the data it is apparent that the orientation of the C-3 and/or C-11 substituent can be tentatively related to the variation of the 19-H–F coupling constant. Thus, if the substituent bond dipole is roughly parallel to the C–F or C_{10}–C_{19} bond axis (*i.e.*, axial substituents) then $J_{19H,6\beta F}$ is increased. Conversely, for substituent bond dipoles approximately at right angles to this axis (*i.e.*, for substituent groups in the general plane of the steroid) a small decrease of the 19-H–F coupling constant is observed. Moreover the increments of $J_{19H,6\beta F}$ decrease or increase are roughly additive. A consideration of specific substituent groups exemplifies these conclusions.

Introduction of a C-3 keto group in place of 3β acetate or hydroxyl reduces $J_{19H,6\beta F}$ from *ca.* 4.5 to *ca.* 3.7 c.p.s. (−0.8 c.p.s.). Inspection of section B shows that introduction of 11-carbonyl causes a similar reduction, from 5–5.2 down to 4.2–4.6 c.p.s. (*ca.* −0.7 c.p.s.). These effects are roughly additive for the sole 3,11-diketone studied (Table II, section D), for which a fall of *ca.* 2 c.p.s. for $J_{19H,6\beta F}$ is registered in comparison with

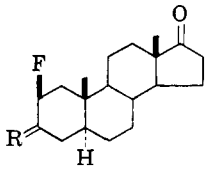
to ±1 c.p.s. Coupling constants, J, also quoted in c.p.s. units, are accurate to ±0.5 c.p.s. For all spectra a 60 Mc.p.s. oscillator frequency was employed. Thanks are due to the Universidad Nacional de México and the University of Texas for time on Varian A-60 instruments and to Mr. P. W. Landis, Eli Lilly and Co., Indianapolis, for several spectra on a Varian HR-60 spectrometer. No attempts are made to allocate signs to coupling constants.

(13) Values of r were measured from Barton molecular models.[14] Three separate models of each type of substituted steroid were assembled and two measurements of r were recorded from each model. Each value of r shown in Table II is therefore the arithmetical mean of six measurements. These values probably are in error by less than 10%. The models do not take account of the slight distortion of ring B owing to the nonbonded 1,3-diaxial fluorine–methyl interaction.

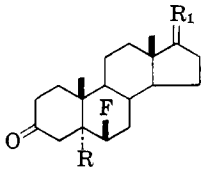
(14) D. H. R. Barton, *Chem. Ind.* (London), 1136 (1956).

coupling constants of the steroid diols and diol monoacetates listed in section A. Conversely a cycloethylene ketal group at C-3 (Table II, section B) causes an increase of *ca.* 0.8 c.p.s. in $J_{19H,6\beta F}$ relative to the 3β-hydroxy-(or acetoxy)-11-unsubstituted analogs (section A). The concept of coupling constant increment additivities finds further support in a study of compounds XXIV and XXV. A 6β-fluorosteroid-3β,5α-diol, or the 3-acetate, shows $J_{19H,6\beta F}$ 4.5 c.p.s. Introduction of an 11-ketone lowers the coupling constant by *ca.* 0.7 c.p.s. while change to a 3-ethylene ketal group raises the *J*-value by *ca.* 0.8 c.p.s. (*vide supra*). Thus compounds XXIV and XXV should have $J_{19H,6\beta F}$ values of *ca.* 4.5 − 0.7 + 0.8 = *ca.* 4.6 c.p.s. This figure is in good agreement with the observed values (Table II, section B).

There remained, however, one further fact which had to be rationalized if the concept of additivity were valid. The gratifyingly narrow range of $J_{19H,6\beta F}$ values given in section A of Table II conflicted sharply with the recorded values of $J_{19H,6\beta F}$, 2 c.p.s. for 2β-fluoro-3α-hydroxy-5α-androstan-17-one (XXXI) and the corresponding 3-ketone XXXII.[15] The sole structural differences between the 2β-fluoro-3-ketone compound XXXII and 6β-fluoro-5α-hydroxyandrostane-3,17-di-



XXXI, R = α-OH, β-H
XXXII, R = O



XXVIII, R = H; R_1 = α-H, β-OAc
XXX, R = OH; R_1 = O

one (XXX) are in the site of substitution of fluorine and the presence of a 5α-hydroxyl substituent in the 6β-fluoro derivative. Though Allinger and co-workers have drawn attention to a small distortion of ring A from a true chair form in 2β-fluoro steroids,[16] it was necessary to check whether this could effect the whole of the observed reduction in $J_{19H,F}$ from 3.7 (XXX) to 2 c.p.s. (XXXII), especially since a similar 1,3-diaxial nonbonded interaction of 6β-fluorine and the angular 10β-methyl exists which will slightly deform ring B. The principal cause of the different $J_{19H,F}$ values between compounds XXXII and XXX, and between XXXI and the analogous 3β-hydroxy-6β-fluoro derivatives XXVII and XXIX, appears to be the 5α-electronegative substituent of the 6β-fluorosteroids. This was dramatically revealed on examination of 6β-fluoro-17β-hydroxy-5α-androstan-3-one acetate (XXVIII)[17] where $J_{19H,6\beta F}$ falls to 2.2 c.p.s. It is clear that, whatever the mechanism of H–F coupling, the 3-keto group in compounds XXVIII and XXXII has a very similar effect upon the magnitude of $J_{19H,2\beta F}$ and $J_{19H,6\beta F}$ (*vide infra*). The effect of the polar 5α-bond is to augment the magnitude of $J_{19H,6\beta F}$ by *ca.* 1.5 c.p.s. Table III summarizes the additive increments of $J_{19H,6\beta F}$ due to various substituents on rings A or C. Increases due to

(15) P. D. Klimstra and R. E. Counsell, *J. Med. Pharm. Chem.*, **5**, 1216 (1962).

(16) N. L. Allinger, M. A. DaRooge, M. A. Miller, and B. Waegell, *J. Org. Chem.*, **28**, 780 (1963).

(17) Prepared by Dr. L. H. Knox in these laboratories through hydrogenation of 6β-fluorotestosterone over palladium-on-charcoal, followed by acetylation. The 5α-configuration was proved by o.r.d. (positive Cotton effect curve).

TABLE III

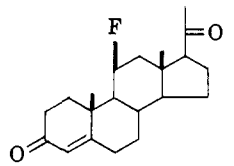
$J_{19H,6\beta F}$ COUPLING CONSTANT ADDITIVE INCREMENTS OWING TO SUBSTITUENT GROUPS[a]

Group	$J_{19H,6\beta F}$, increment, c.p.s.
5α-OH	+1.5
5α-Br	+1.5
3-Ketone	−0.8
11-Ketone	−0.7
11β-OH	+1.8
3-Cycloethylene ketal	+0.8

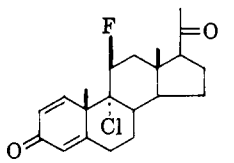
[a] All values are relative to a hypothetical 3β-acetoxy-6β-fluorosteroid bearing no other substituents in rings A, B, or C, and for which $J_{19H,6\beta F}$ = 3.0 c.p.s. [2.2 (XXVIII) + 0.8 c.p.s. (3-C=O → 3β-OAc effect)].

axial substituents seem to be generally larger than the decreases for substituents in the plane of the ring system. The 3-cycloethylene ketal group with both equatorial and axial C–O bonds leads to a net increase of $J_{19H,6\beta F}$. However, it is to be emphasized that these observations concerning additivity have been made for a few compounds only and a more extensive examination is required before the apparent additivity of coupling constant increments could be accepted as established.

It has been shown above that in the absence of axial electronegative substituents on the connecting σ-bond chain the coupling constants $J_{19H,2\beta F}$ and $J_{19H,6\beta F}$ are approximately equal, *ca.* 2 c.p.s. Since a closely similar geometry is involved for 4β-, 8β-, and 11β-fluoro derivatives, it might be expected that, in the absence of neighboring electronegative substituents, the $J_{19H,F}$ values for each of these fluorines should also be of the same order of magnitude. Actually, in the 11β-fluoro compounds the fluorine is slightly closer to the 19-protons than is fluorine at any of the other positions mentioned. Ayer reported for 11β-fluoropregn-4-ene-3,20-dione (XXXIII) $J_{18H,11\beta F}$ 3 and $J_{19H,11\beta F}$ 3 c.p.s.,[18] values which match very well. $J_{19H,6\beta F}$ (calcd.) when neighboring electronegative groups are absent (*vide supra*). We determined for 11β-fluoro-9α-chloro-preg-



XXXIII



XXXIV

na-1,4-diene-3,20-dione (XXXIV)[19] $J_{18H,11\beta F}$ 2.7 and $J_{19H,11\beta F}$ 5.3 c.p.s.[1b] Comparison of coupling constants shows that whereas the introduction of the electronegative 9α-chlorine substituent has only a small effect on the magnitude of $J_{18H,11\beta F}$ it leads to a substantial increase in $J_{19H,11\beta F}$.[20] Even allowing for experimental error and that the n.m.r. spectra of XXXIII and XXXIV were recorded by separate investigators it seems that the 9α-chlorine changes $J_{18H,11\beta F}$ by considerably

(18) D. E. Ayer, *Tetrahedron Letters*, 1065 (1962).

(19) Sample very kindly supplied by Dr. E. P. Oliveto; *cf.* H. Reimann, E. P. Oliveto, R. Neri, M. Eister, and P. Perlman, *J. Am. Chem. Soc.*, **82**, 2308 (1960).

(20) The change from a Δ^4-3-keto system (XXXIII) to a $\Delta^{1,4}$-3-ketone (XXXIV) results in a further flattening of ring A. Models[14] show that the 11β-F–18-H distance[13] is substantially unaltered and the 11β-F–19-H distance[12] is slightly smaller (<5%) as a result. The extra ring A double bond in XXXIV probably makes some contribution to the change in $J_{19H,11\beta F}$, but from the known effects of axial 5α-bromo or hydroxy it is reasonable to suppose that it is the equivalent axial 9α-chloro group in XXXIV which is primarily responsible in this case.

less than 1 c.p.s. Thus it is concluded that an electronegative substituent sited on the σ-bond chain between the two coupling nuclei in these fluorosteroids *raises* the magnitude of the coupling constant.[21] Other electronegative substituents may effect the coupling constant to a lesser extent but perhaps for different reasons (*vide infra*).

The possible coupling mechanisms may now be evaluated in the light of the above information. Diminution in J-values owing to carbonyl at C-3 or C-11 is explicable on the basis of a through-bonding-electrons coupling mechanism. It is quite conceivable that ring-B strain is set up by introduction of sp^2-carbon at one or both positions, thus leading to reduced orbital overlap along the chain of bonds connecting the coupling nuclei. That such strains are induced in rings distant from the site of structural change has been well-established through the work of Barton and his collaborators on the long-range conformational transmission effect.[22] This must involve torsion of the bonds connecting skeletal carbons and, in consequence, a series of small changes in bond angles is induced. Furthermore, electronegative substituents distant from the chain of bonds connecting the coupling nuclei can induce positive charge on one or more carbon atoms in the chain, an effect demonstrated above to lead to changes in $J_{19H,F}$. Introduction of 11β-substituents is known to cause severe steric interactions across the β-face of the molecule. An 11β-hydroxyl group leads to more ring strain than does a 3-cycloethylene ketal. In this respect it is pertinent to note that the 11β-hydroxyl group is the only substituent found so far to change $J_{19H,6\beta F}$ as markedly as an electronegative substituent on the C_6–C_5–C_{10}–C_{19} chain itself (*cf.* Table III). Additivity of $J_{19H,6\beta F}$ increments associated with various substituent groups is also in accord with the concept of induced ring strain and bond angle changes in the interconnecting chain. Additivity would be expected if the strains induced by the distant substituent groups could augment or cancel each other. However, in spite of the fact that the variation in $J_{19H,6\beta F}$ may be rationalized on the basis of a through-bonding-electrons coupling mechanism these explanations offer no clue as to why the converging-vector rule is valid experimentally.

Coupling by orbital overlap across space does provide a physical expression of the converging-vector rule.[23] The widely differing effects of electronegative substituent groups on the magnitude of $J_{19H,6\beta F}$ can no longer be satisfactorily explained on the basis of altered bond angles since the 19-H–6β-F internuclear distance, r,[13] varies only slightly for the compounds listed in sections A–D of Table II. Some direct effect of nearby substituent electronegative groups upon the extent of proton and fluorine orbital overlap across space must exist if the through-space mechanism operates. Neighboring polar bonds could influence the appropriate proton and fluorine orbitals by induction of charge or by a direct field effect. In neither case has the magnitude of the orbital perturbation been calculated. However, three pieces of experimental evidence offered above are distinctly compatible with this concept of orbital distortion. A 5α-electronegative substituent raises the value of $J_{19H,6\beta F}$. This could be caused by an effect upon either one, or both, of the 19-proton and fluorine orbitals. But a 9α-chlorine substituent raises $J_{19H,11\beta F}$ substantially while exercising a negligible effect on $J_{18H,11\beta F}$. If the 9α-chlorine distorted the fluorine atomic orbitals, then coupling constants with *both* 18- and 19-protons should be affected. Since this is not the case, it would be necessary to conclude that the electronegative 9α-chlorine causes perturbation of the nearby 19-proton orbitals, but is too distant from the 18-protons to bring about a comparable change. This interpretation also fits well the observed effects of polar 11β-hydroxyl and 5α-hydroxyl or bromine substituents. Furthermore, it was noted that in the presence of a 3-keto group $J_{19H,2\beta F}$ and $J_{19H,6\beta F}$ have almost identical values in the absence of other proximate electronegative substituents. This fact is readily comprehensible if the carbonyl dipole exerts its effect only by 19-proton orbital perturbation. Conversely, if fluorine orbitals were distorted, one might expect the 2β-fluorine to reflect a much stronger influence by neighboring 3-carbonyl than would the more distant 6β-fluorine. The value of $J_{19H,2\beta F}$ is apparently unchanged on substitution of 3-keto by 3α-hydroxyl[15] which again suggests that a distant polar group has only a small, or negligible, effect upon distant angular methyl proton orbitals.

In conclusion it has to be recognized that the evidence accumulated so far does not point overwhelmingly in favor of either possible mechanism. Indeed both modes of coupling may be in operation, though to differing extents. The applicability of the converging-vector rule does tend to give credence to the through-space coupling mechanism, but definitive evidence still awaits discovery.

The approach to the problem of long-range proton–fluorine coupling pursued in this work has been purely empirical. It is nevertheless instructive to make comparisons with recent work on fluorine–fluorine coupling in saturated organic compounds. Petrakis and Sederholm[25] have concluded that such fluorine–fluorine couplings take place primarily through space. Further experimental evidence supporting the concept of a through-space contribution was provided by Rogers and Graham,[26] but the earlier reasoning[25] has been both challenged[27,28] and buttressed.[29] It is clear that in certain respects proton–fluorine coupling represents a position half-way between the simpler proton–proton and complex fluorine–fluorine coupling phenomena. The greater rigidity of the fluorosteroids obviates the need to make assessment of rotamer contributions.[25–29] McConnell's analysis of the couplings in C_2F_4 using molecular or-

(21) Mr. T. A. Wittstruck, Clark University, has very kindly informed us that, working in a different field, he has observed a similar phenomenon. However, the literature contains numerous examples of coupling constant *diminution* by similarly sited electronegative substituents. Such contrasts could reflect different signs of coupling constants, or other factors.

(22) D. H. R. Barton, F. McCapra, P. J. May, and F. Thudium, *J. Chem. Soc.*, 1297 (1960), and earlier papers in the series.

(23) Dr. G. Slomp has concluded, from a study of fluorinated benzphenanthrenes, that the spatially proximate fluorine and proton couple through the bonds rather than through space.[24] However, since long-range coupling through extended σ-bond systems is rarer and of lesser magnitude than for π-bonds this conclusion cannot properly be extended to saturated systems. The author wishes to acknowledge a friendly exchange of correspondence with D. Slomp and a copy of the relevant paper[24] prior to publication.

(24) M. S. Newman, R. G. Muetzer, and G. Slomp, *J. Am. Chem. Soc.*, **85**, 4018 (1963).

(25) L. Petrakis and C. H. Sederholm, *J. Chem. Phys.*, **35**, 1243 (1961).

(26) M. T. Rogers and J. D. Graham, *J. Am. Chem. Soc.*, **84**, 3666 (1962).

(27) J. I. Musher, *J. Chem. Phys.*, **36**, 1086 (1962).

(28) R. K. Harris and N. Sheppard, *Trans. Faraday Soc.*, **59**, 606 (1963).

(29) L. Petrakis and C. H. Sederholm, *J. Chem. Phys.*, **36**, 1087 (1961).

bital theory showed that here the coupling constants could be calculated by considering contributions from magnetic dipolar and electron-orbital terms only.[30] These are likely to be important factors in any analysis of coupling involving only one fluorine also. The apparent dependence of both fluorine–fluorine and proton–fluorine couplings on spatial factors suggests that a mathematical treatment of either phenomenon must also aid our understanding of the other.

Acknowledgment.—The author is indebted to Professor M. Karplus, Columbia University, for invaluable correspondence and discussion on sundry theoretical aspects of coupling mechanisms.

(30) H. M. McConnell, *J. Chem. Phys.*, **24**, 460 (1956).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY, CHICAGO 16, ILL.]

The Transmission of Electronic Effects. The ρ–ρ Relation in the Reaction of Phenylpropionic Acids with Diphenyldiazomethane[1]

BY RORY A. MORE O'FERRALL AND SIDNEY I. MILLER

RECEIVED FEBRUARY 18, 1964

Rate data for the reactions of ten phenylpropionic acids (p-$(CH_3)_2CH$, p-CH_3, p-CH_3O, 3,4-$(CH_3O)_2$, H, p-F, m-HO, p-Br, m-Cl, p-NO_2) with diphenyldiazomethane (DDM) in ethanol have been obtained. The entropies of activation ($-\Delta S^* = 6$–15 e.u.) are proportional to the enthalpies of activation ($\Delta H^* = 12.7$–15.4 kcal. mole^{-1}) in this series with a slope of *ca.* 260°. Acceptable Hammett lines have been obtained for k in l. mole^{-1} min.$^{-1}$ at 26.05°, $\log k = 0.18\sigma - 0.226$ and at 35.35°, $\log k = 0.17\sigma + 0.1105$. Taking ρ from the dissociation of the acids RGCOOH and ρ' from the rate constants of these acids with DDM, one obtains satisfactory test comparisons in the form $\rho/\rho' =$ constant. Alternatively, the attenuation factor for phenylpropionic acids or esters relative to corresponding benzoic derivatives is $\epsilon = 0.22$ for four different reactions. Despite their utility, it does not yet seem possible to provide a rigorous theoretical basis for these ρ–ρ relations.

In this paper we continue our inquiry into the factors which affect the relay of electronic influences from a substituent R to a reaction site S in a species R–G_i–COS. Previously, it was shown that two substantially equivalent ρ–ρ relations

$$\rho_{R\text{-}G\text{-}COOH}/\rho_{R\text{-}G\text{-}COS} = \pi \qquad (1)$$

$$\rho_{R\text{-}G\text{-}COS}/\rho_{RC_6H_4COS} = \epsilon \qquad (2)$$

were useful in examining the alterations in the Hammett ρ as the reaction type changed but the interposed group G remained the same (eq. 1), or as the reaction type remained unchanged but the interposed group G varied (eq. 2).[2–5] π is a measure of the ability of a substituent to communicate electronic effects to a given site for a given reaction (*e.g.*, ester hydrolysis compared to a standard reaction, *i.e.*, acid dissociations in water at 25°) and ϵ is a measure of the attenuation of an electronic effect through G as compared with the group $-C_6H_4-$.[4–6]

Together with acid dissociation of acids RGCOOH or the basic hydrolysis of their esters, the reactions of the acids with diphenyldiazomethane (DDM) have attained the status of a standard or probe process in structure reactivity studies.[3–5,7] To test eq. 1 and 2 we have accumulated rate data on several acid families in this reaction

$$\begin{array}{l} R\text{—}G\text{—}COOH \\ + \\ (C_6H_5)_2CN_2 \end{array} \xrightarrow[-N_2]{} \begin{cases} \xrightarrow{} R\text{—}G\text{—}COOCH(C_6H_5)_2 \\ \xrightarrow[C_2H_5OH]{} (C_6H_5)_2CHOC_2H_5 \end{cases} \qquad (3)$$

Here rate data are reported for several phenylpropionic acids in process 3 and the problem of attenuation of the substituent effect by G is considered. Because its reaction site is "insulated" from the substituent, the phenylpropionic system is of particular interest in theories of the influence of structure on reactivity.

Results and Discussion

Rate data for the reactions of the phenylpropionic acids with DDM are given in Table I. For a wide range of substituents the total variation in the rates is small at 1.6. As in the DDM reactions with the phenylacetic[3] and *trans*-cinnamic[4] acids the activation entropies and enthalpies are proportional; here the slope

TABLE I

RATE CONSTANTS AND ACTIVATION PARAMETERS FOR THE REACTION:

$$RC_6H_4CH_2CH_2COOH + (C_6H_5)_2CN_2 \xrightarrow{C_2H_5OH} RC_6H_4CH_2CH_2COOCH(C_6H_5)_2 + C_2H_5OCH(C_6H_5)_2 + N_2$$

R	k, l. mole^{-1} min.$^{-1}$ [a,b] 26.05 ± 0.1°	35.35 ± 0.1°	ΔH^* ± 1.0, kcal. mole^{-1}	$-\Delta S^*$ ± 3.0, cal. deg.$^{-1}$ mole^{-1}
p-i-C_3H_7	0.52			
p-CH_3	.54	1.18	14.4	9.3
p-CH_3O	.56	1.11	12.7	14.9
3,4-$(CH_3O)_2$	.55	1.22	15.0	7.3
H	.58[c]	1.21	13.7	11.5
p-F	.63			
m-HO	.54	1.22	15.4	5.7
p-Br	.64	1.44	15.3	6.4
m-Cl	.68	1.50	15.0	7.7
p-NO_2	.85	1.77	13.6	12.7

[a] Average deviation less than 2%. [b] Average of three runs except as indicated. [c] Average of four runs.

(1) Supported by the U. S. Army Research Office (Durham).

(2) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

(3) R. A. M. O'Ferrall and S. I. Miller, *J. Am. Chem. Soc.*, **85**, 2440 (1963).

(4) J. D. S. Ritter and S. I. Miller, *ibid.*, **86**, 1507 (1964).

(5) W. K. Kwok, R. A. More O'Ferrall, and S. I. Miller, *Tetrahedron*, **20**, 1913 (1964).

(6) M. Charton, *J. Org. Chem.*, **26**, 735 (1961).

(7) J. D. Roberts and R. A. Carboni, *J. Am. Chem. Soc.*, **77**, 5554 (1955); I. Solomon and R. Filler, *ibid.*, **85**, 3492 (1963); J. Hine and W. L. Bailey, *ibid.*, **81**, 2075 (1959); W. F. Little and R. Eisenthal, *ibid.*, **83**, 4936 (1961); C. K. Hancock and J. S. Westmoreland, *ibid.*, **80**, 545 (1958); R. Benkeser, C. E. de Boer, R. E. Robinson, and D. M. Sauve, *ibid.*, **78**, 682 (1956); R. W. Taft, Jr., and D. J. Smith, *ibid.*, **81**, 2075 (1959); N. B. Chapman, J. Shorter, and J. H. P. Utley, *J. Chem. Soc.*, 1824 (1962); A. Buckley, N. B. Chapman, and J. Shorter, *ibid.*, 178 (1963); O. Exner, *Tetrahedron Letters*, 815 (1963); A. Tavlik, P. Zuman, and O. Exner, *Collection Czech. Chem. Commun.*, **29**, 1266 (1964).