Substituent Effects. VI.[1,2] Fluorine Nuclear Magnetic Resonance Spectra of 3′- and 4′-Substituted 4-Fluorobiphenyls and 3″-Substituted 4-Fluoroterphenyls

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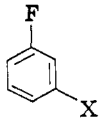
Abstract: Derivatives of 4-fluorobiphenyl with a variety of substituents in the 3′ and 4′ positions, and derivatives of 4-fluoroterphenyl with substituents in the 3″ position, have been synthesized and their fluorine nmr spectra have been measured. The chemical shifts for the biphenyls correlate well with σ constants calculated by the *FM* method,[4] while comparison with results for the corresponding terphenyls provides further support for the idea[4] that the long-range interactions in such compounds are due to field effects rather than σ-inductive effects. Comparison with the chemical shifts in *meta*-substituted fluorobenzenes suggests that the latter are out of step with the effects of substituents on other side-chain properties, and suggests that some of the conclusions that have been drawn from nmr data for substituted benzenes may have been incorrect.

Previous papers of this series[2,4] presented evidence suggesting that the σ-inductive effect of a substituent is unimportant at atoms separated by more than one bond from the atom to which the substituent is attached. Long-range interactions seem to be due solely to the field effect, or to the polarization of π electrons in intervening conjugated systems (mesomeric effect), the σ-inductive effect being rapidly attenuated with distance. On this basis a simple treatment (*FM* method) was developed[4] for calculating the effects of a variety of substituents on the pK_A of α-naphthoic acid, and recent studies of substituented β-naphthoic acids have shown that the same is true of this system also.[5]

The *FM* method is, however, admittedly a very crude approximation in that it assumes that the field effect of a dipolar substituent falls off inversely as the distance between it and the reaction center. While it is true[4] that an inverse second-order dependence would not be expected since this law applies only to point dipoles in a medium of uniform dielectric constant, the assumption[4] that the field due to one end of the dipole is damped out by the solvent is certainly much too extreme. Recent studies by Stock and his collaborators[6] on the effects of substituents in the bicyclooctane system have indeed shown that the situation is best treated as one involving two separated point charges of equal and opposite sign at the ends of the dipole, a different effective dielectric constant being used in calculating the field at the reaction center due to each of the charges.

The purpose of the present investigation was twofold. First, we wanted to get more evidence concerning the way the effect of an inductive substituent diminishes with distance; secondly, we wanted to see if the chemical shifts of the fluorine nmr spectra of organic fluorides could be used generally as a measure of substituent effects. Gutowsky and his collaborators[7] showed some time ago that the effect of substituents on the nmr chemical shifts of fluorine in fluorobenzene followed roughly the Hammett $\rho\sigma$ relation, and recently Taft and his collaborators[8] have studied the fluorobenzene system in great detail. However little work has been done on other ring systems, and the results for benzene are anomalous in certain respects; thus the effect of substituents in the *meta* position of fluorobenzene seems[8] to follow σ_I rather than σ_m. For our purpose we needed data for the effects of a variety of substituents on the fluorine nmr chemical shifts of a series of fluoro compounds in which the geometrical distance between substituent and fluorine is clearly defined. Since we were interested primarily in the field effect rather than the mesomeric effect, it was also important that there should be no direct resonance interaction (mutual conjugation) between the substituent and fluorine. These considerations led us to compare the following series of compounds: 3-substituted fluorobenzenes (I), 3′-substituted 4-fluorobiphenyls (II), and 3″-substituted 4-fluoroterphenyls (III). Rotation about the interannular bonds of II or III does not alter the distance from substituent to fluorine, and the *meta* orientation should inhibit mutual conjugation between them.



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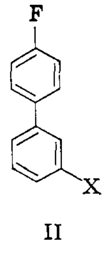

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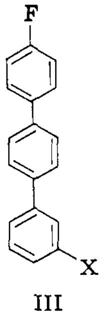

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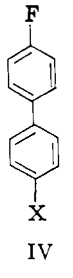

IV

Synthetic Procedures

The *meta*-substituted fluorobenzenes (I) are all well-known compounds and their fluorine nmr spectra have been exhaustively studied by Taft, *et al.*[8]

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[1] This work was supported by the Army Research Office (Durham) through Grant DA-AROD-31-124-G713.

[2] Part V: M. J. S. Dewar and A. P. Marchand, *J. Am. Chem. Soc.*, in press.

[3] NASA Predoctoral Fellow, 1962–1964; National Institutes of Health Predoctoral Fellow, 1964–1965.

[4] M. J. S. Dewar and P. J. Grisdale, *J. Am. Chem. Soc.*, **84**, 3548 (1962).

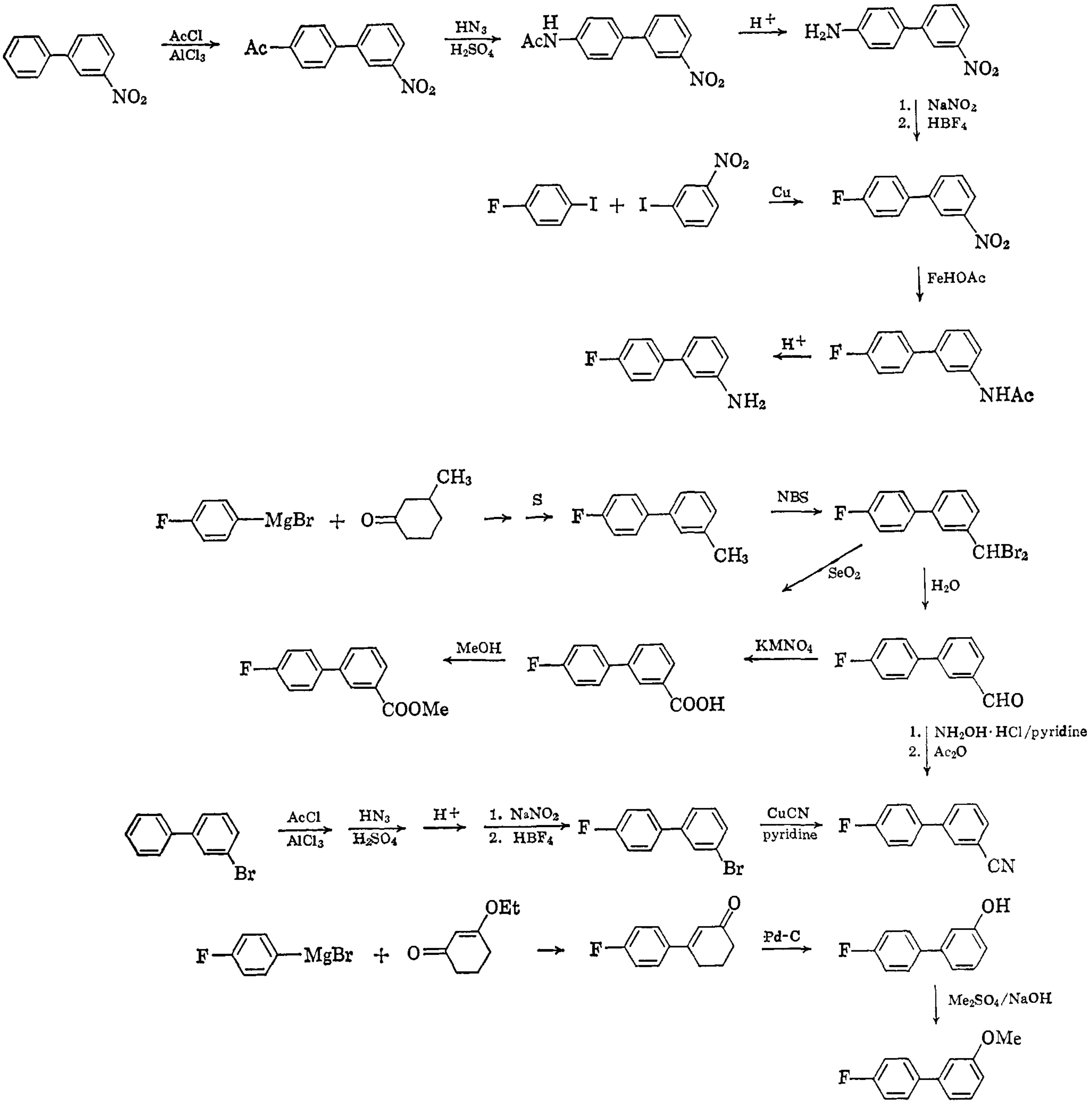
[5] W. Adcock and P. R. Wells, *Australian J. Chem.*, **18**, 1351 (1965).

[6] H. D. Holtz and L. M. Stock, *J. Am. Chem. Soc.*, **86**, 5188 (1964); **87**, 2404 (1965).

[7] H. S. Gutowsky, D. W. McCall, B. R. McGravey, and L. H. Meyer, *ibid.*, **74**, 4809 (1952).

[8] (a) R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Andersen, and G. T. Davis, *ibid.*, **85**, 709, 3146 (1963); (b) R. W. Taft and L. D. McKeever, *ibid.*, **87**, 2489 (1965).

Scheme I. 4-Fluoro-3′-Substituted Biphenyls



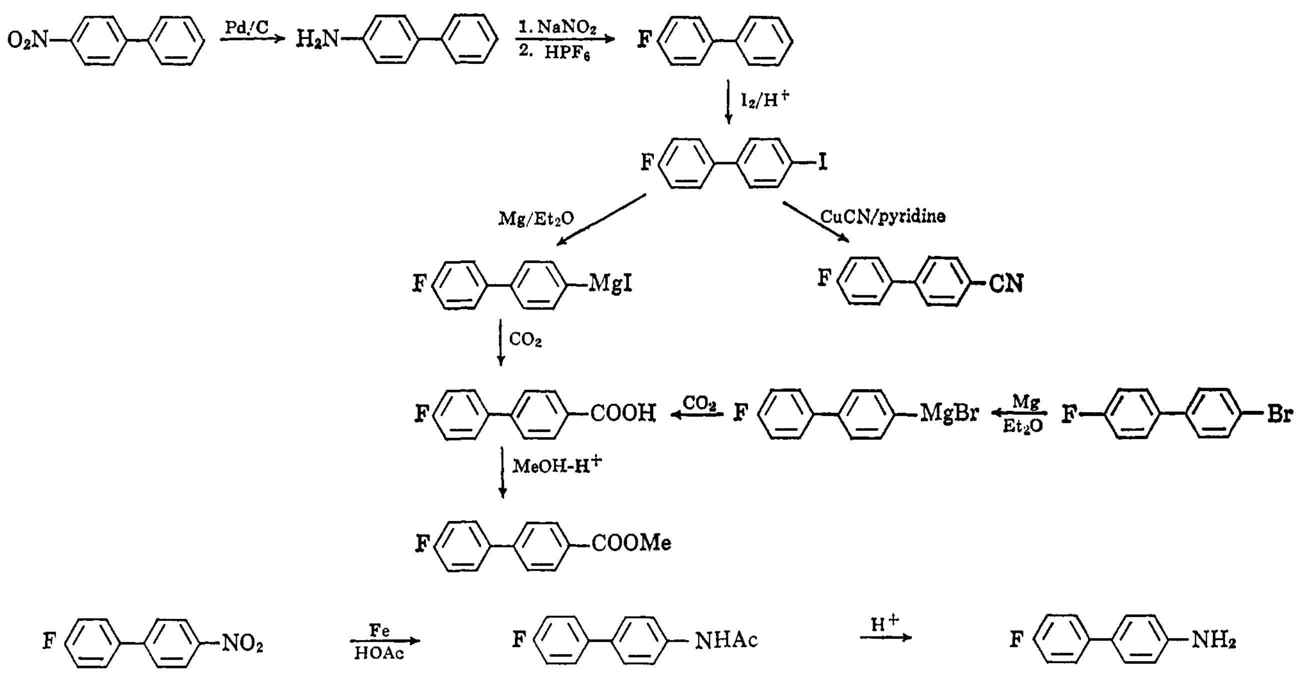
Most of the 3′-substituted 4-fluorobiphenyls were new compounds; the methods of synthesis, which followed established methods, are indicated in Scheme I. We also prepared a number of 4′-substituted 4-fluorobiphenyls (IV) by the methods indicated in Scheme II. The terphenyls (III) proved unexpectedly awkward to synthesize; reactions which proceeded in good yield in the biphenyl series frequently failed for no very clear reason in the case of the terphenyls. A number of derivatives were, however, eventually obtained by the procedures shown in Scheme III.

Measurement of Fluorine Nmr Spectra

The fluorine nmr spectra were measured with a Varian DP60 spectrometer with a variable-temperature probe operating at 56.4 Mc, using solutions containing 20% (w/w) of the fluoro compound together with 5% (w/w) of 1,1,2,2-tetrachloro-3,3,4,4-tetrafluorocyclobutane (TCTFB) as internal standard. The spectra were calibrated using a Hewlett-Packard 200 JR audio-oscillator, and each spectrum was swept at least four times in each direction at a maximum rate of 15–20 cps/sec. Chemical shifts were calculated for the center of each F^{19} multiplet; the standard deviations of the 4-fluorobiphenyls and 4-fluoroterphenyls were nearly all less than 4 cps; a further check was provided by comparison with data for some of the 4′-substituted 4-fluorobiphenyls (IV) kindly communicated to us by Professor Robert W. Taft, Jr.; our results agreed with his to within 0.02 ppm which is well within our estimated limits of experimental error (see Table I).

Most of the biphenyls were measured in benzene at 36°; however some of the more polar compounds (*e.g.*, those with X = COOH, NH, or NHAc) were not suffi-

Scheme II. 4-Fluoro-4′-Substituted Biphenyls



Scheme III. 4-Fluoro-3″-Substituted Terphenyls

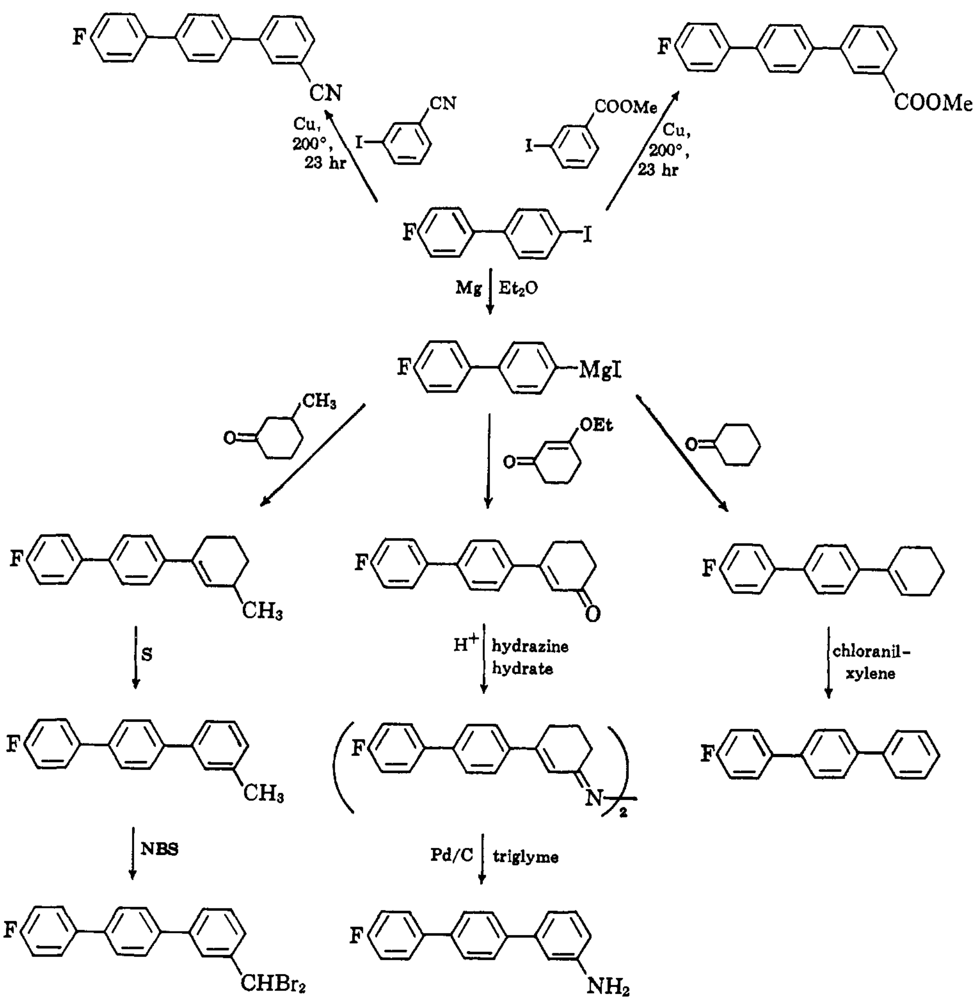


Table I. Substituent Chemical Shifts for 3′- and 4′-Substituted Biphenyls

Substituent	Solvent	Temp., °C	δ^{TCTFB},[a] cps	*SCS*[b]	σ_{ij}[c]
None	Benzene	36	126.4 ± 2.0	0	0
	DMF	36	160.9 ± 4.6	0	0
	DMF	99.2	184.8 ± 2.6	0	0
4′-NO$_2$	Benzene	36	−28.0 ± 1.2	−2.74 (−2.73[d])	0.28
	DMF	36	8.1 ± 0.5	−2.72	
	DMF	63.7	12.1 ± 1.2	−2.82[e]	
	DMF	75.5	26.5 ± 1.8	−2.65[e]	
4′-CN	Benzene	36	0.0	−2.24	0.23
3′-NO$_2$	Benzene	36	9.0 ± 0.9	−2.08	0.27
3′-CN	Benzene	36	24.7 ± 1.0	−1.80	0.21
4′-COOH	DMF	95.3	105.9 ± 1.8	−1.37[e]	0.16
3′-Br	Benzene	36	62.4 ± 2.7	−1.13	0.15
4′-COOMe	Benzene	36	68.9 ± 2.8	−1.02	0.16
3′-CHBr$_2$	Benzene	36	72.0 ± 2.6	−0.97	. . .[f]
4′-I	Benzene	36	76.1 ± 2.3	−0.90	0.10
3′-COOMe	Benzene	36	80.5 ± 1.4	−0.81	0.14
3′-COOH	DMF	36	115.6 ± 3.6	−0.80	0.14
4′-Br	Benzene	36	82.4 ± 2.0	−0.78 (−0.80[d])	0.11
3′-OH	Benzene	36	103.3 ± 1.7	−0.41	0.05
3′-NHAc	DMF	36	148.3 ± 2.2	−0.22	0.08
3′-OMe	Benzene	36	114.6 ± 1.0	−0.21	0.04
4′-F	Benzene	36	118.5 ± 3.1	−0.14 (−0.12[d])	0.06
3′-Me	Benzene	36	134.0 ± 3.1	+0.14	−0.03
3′-NH$_2$	DMF	36	187.8 ± 4.1	0.48	−0.06
4′-NHAc	DMF	36	190.8 ± 1.6	0.53	0.03
4′-NH$_2$	DMF	36	293.0 ± 4.8	2.34	−0.17

[a] Chemical shift relative to TCTFB in cps; listed errors are standard deviations for at least eight measurements (see text). [b] Substituent chemical shift, in ppm. [c] Calculated using *F* and *M* parameters in ref 8. [d] Measurements by Dr. R. G. Pews, kindly communicated to us by Professor R. W. Taft. [e] Value for 4-fluorobiphenyl interpolated. [f] *F* and *M* parameters not available, since σ_m and σ_p not known.

ciently soluble in benzene and their spectra were therefore measured in dimethylformamide (DMF) at higher temperatures. Taft, *et al.*,[8] have found that changes in the chemical shift of fluorine in *meta*-substituted fluorobenzenes are almost independent of the solvent and temperature, provided that there are no complications due to hydrogen bonding; the results for 4′-nitro-4-fluorobiphenyl shown in Table I suggest that the same is true for the fluorobiphenyls. It is, however, necessary to compare the substituted and unsubstituted fluoro compounds under the same conditions; for the difference between a given fluoro compound and TCTFB is *not* invariant.

Table I lists the fluorine nmr results for the two series of substituted 4-fluorobiphenyls, II and IV. The fifth column shows the substituent chemical shifts, *i.e.*, the differences (in ppm) between the chemical shift of the compound and that of 4-fluorobiphenyl, in the same solvent and at the same temperature. The comparisons could not all be made under the same conditions because of lack of solubility; this was unfortunate since, as Taft, *et al.*,[8] have shown, substituent chemical shifts can be affected by change of solvent if there are direct interactions between this and the substituent.

Table II shows similar values for the 3′′-substituted 4-fluoroterphenyls. Here problems due to insolubility were severe. The substituent chemical shifts, with one exception, were therefore derived from comparisons with 3′′-methyl-4-fluoroterphenyl which is much more soluble than 4-fluoroterphenyl itself. Direct comparison showed that the substituent chemical shift of the methyl derivative is zero, within the limits of experimental error. Various practical reasons made it impossible for us to measure the chemical shift of 3′′-amino-4-fluoroterphenyl at the same temperature (99.2°) as that used for 4-fluoroterphenyl; the substituent chemical shift was therefore estimated indirectly in two ways: firstly, by comparison with the corresponding dibromomethyl derivative (*SCS* = 0.13); secondly, by extrapolation of the chemical shift of the amino derivative (relative to TCTFB) to 99.2°, and comparison with 4-fluoroterphenyl (*SCS* = 0.09). The value (0.11) listed in Table II is the mean of these. This extrapolation seems to be justified by the data for 4′-nitro-4-fluorobiphenyl in Table I.

Table II. Substituent Chemical Shifts for 3′′-Substituted 4-Fluoroterphenyls

Substituent	Solvent	Temp, °C	δ^{TCTFB},[a] cps	*SCS*[a]	σ_{ij}[a]
None	DMF	99.2	175.8 ± 3.5	0	0
CN	Benzene	36	75.4 ± 1.4	−0.74	0.13
CHBr$_2$	Benzene	36	91.8 ± 1.5	−0.45	. . .
	DMF	89.4	158.5 ± 4.0		
COOMe	Benzene	36	100.7 ± 1.6	−0.26	0.08
CH$_3$	Benzene	36	117.4 ± 1.1	0.00	0.00
	DMF	99.2	173.8 ± 5.3		
NH$_2$	DMF	36	154.2 ± 2.2	0.11	−0.04
	DMF	89.4	176.8 ± 2.8		

[a] For definition see Table I.

We also included (Table III) a series of 3-substituted fluorobenzenes (I) to ensure that our values for them were determined under the same conditions as those used for the biphenyls and terphenyls; in cases where direct comparison was possible, our values agreed with those of Taft, *et al.*,[8] within the limits of experimental error. Tables I, II, and III also show σ_{ij} constants[9] calculated by the *FM* method;[4] in the case of 3-substituted fluorobenzenes, these are by definition equal to σ_m.

Table III. Substituent Chemical Shifts for 3-Substituted Fluorobenzenes at 36°

Substituent	Solvent	δ^{TCTFB},[a] cps	*SCS*[a]	σ_m[b]
None	Benzene	−38.7 ± 0.9	0	0
	DMF	10.2 ± 0.4	0	0
NO$_2$	Benzene	−219.8 ± 1.8	−3.21 (−3.25[c])	0.71
Br	Benzene	−180.6 ± 1.2	−2.52 (−2.60[c])	0.39
CHBr$_2$	Benzene	−106.4 ± 2.2	−1.20	. . .[d]
HO	Benzene	−102.6 ± 1.3	−1.13	0.12
NHAc	DMF	−37.0 ± 0.5	−0.84	0.21
COOMe	Benzene	−65.0 ± 1.2	−0.47	0.37
COOH	DMF	−12.7 ± 0.8	−0.41	0.37
NH$_2$	DMF	63.9 ± 1.1	0.95	−0.16
CH$_3$	Benzene	28.3 ± 0.7	1.19 (1.15[c])	−0.07

[a] For definition see Table I. [b] D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958). [c] See ref 8a. [d] No σ constant available.

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(9) σ_{ij} is defined as the σ constant for a substituent attached to atom *i* of a given molecule, acting on a center attached to atom *j*.

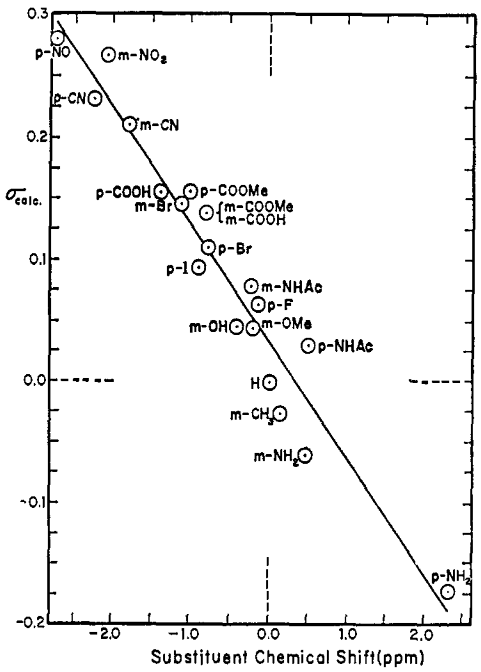


Figure 1. Plot of fluorine substituent chemical shifts for substituted 4-fluorobiphenyls *vs.* σ constants calculated by the *FM* method.[4]

Figure 1 shows a plot of the substituent chemical shifts of the 3′- and 4′-substituted biphenyls against the values of $\sigma_{3'4}$ and $\sigma_{4'4}$ calculated by the *FM* method, the substituent chemical shift being the difference in chemical shift between a given fluorobiphenyl derivative and 4-fluorobiphenyl itself, under comparable conditions. There is a satisfactory linear relation between the two quantities, suggesting that the 3′- and 4′-substituted biphenyls conform to the *FM* relation; this is in agreement with conclusions reached[4] from the limited data available[10] for the effects of 3′ and 4′ substituents on the pK_A of biphenyl-4-carboxylic acid. Indeed, a plot of the substituent chemical shifts *vs.* the pK_A of the corresponding carboxylic acids is linear within the limits of experimental error; in this system the effect of substituents on the chemical shift of fluorine seems to run parallel to their effect on other chemical properties. Moreover the fact that all the points in Figure 1 lie on a common line implies that in this system the substituent chemical shifts are insensitive to changes in the solvent.

The apparently normal behavior of the substituent chemical shifts in 4-fluorobiphenyl is in marked contrast to the abnormal behavior shown by *meta*-substituted fluorobenzenes. As Taft, *et al.*,[8] have pointed out, and as can be seen from the data in Table III, a plot of substituent chemical shifts *vs.* σ_m does not show a satisfactory linear relation between the two quantities. Taft, *et al.*,[8] claim that such a relation does exist between the substituent chemical shifts and σ_I; however it is difficult to see why the effects of substituents on the fluorine chemical shift of fluorobenzene should be so different from their effects on other physical and chemical properties of benzene derivatives, and still harder to see why this abnormal behavior should be confined to fluorobenzene and not apply equally to 4-fluorobiphenyl.

Table IV compares the substituent chemical shifts produced by a given substituent in the 3, 3′, and 3″ positions of fluorobenzene, 4-fluorobiphenyl, and 4-fluoroterphenyl, respectively.

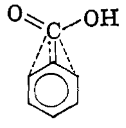
Table IV. Comparison of Substituent Chemical Shifts in Benzene, Biphenyl, and Terphenyl

Substituent[a]	*SCS*(biphenyl)/ *SCS*(benzene)	*SCS*(terphenyl)/ *SCS*(biphenyl)
NO_2	0.65	. . .
CN	0.66[b]	0.39
Br	0.45	. . .
$CHBr_2$	0.80	0.46
COOH	1.98	. . .
COOMe	1.75	0.32
CH_3	0.11	0.0
OH	0.37	. . .
OMe	0.18	. . .
NHAc	0.27	. . .
NH_2	0.50	0.23

[a] In the 3 position of fluorobenzene, 3′ position of 4-fluorobiphenyl, or 3″ position of 4-fluoroterphenyl. [b] Value for 3-fluorobenzonitrile from ref 8a.

It is immediately obvious from these results that something strange is happening in the substituted fluorobenzenes. Thus while the effects of substituents in the 3″ position of 4-fluoroterphenyl are uniformly much smaller than in the 3′ position of 4-fluorobiphenyl, as one would expect, the corresponding ratios for 4-fluorobiphenyl and fluorobenzene not only fluctuate wildly, but in some cases are actually greater than unity—implying that a substituent has a *greater* effect in the 3′ position of 4-fluorobiphenyl than in the *meta* position of fluorobenzene! This result seemed so unreasonable that we checked the values for both series of compounds very carefully; there is no doubt that the effect is real.

We think the explanation must lie in the special nature of the factors underlying the effect of substituents on fluorine chemical shifts. The effect of substituents on most chemical and physical properties of side chains depends on the changes in potential energy due to the production or destruction of charges at the reaction center. These energy differences depend only on the scalar field at the reaction center, and this in turn depends only on the formal charges at various positions in the molecule, and their distances from the reaction center. The effect of charges at atoms *ortho* to the reaction center is therefore comparable with the effect of a charge at the atom to which the reactive side chain is attached. This will be seen clearly from a single example, the effect of a substituent on the acidity of benzoic acid (V); the positions *ortho* to the carboxyl group are not much further away from it than is the carbon atom to which it is attached. The situation is, however, quite different in the case of fluorine chemical shifts in fluorobenzene. Here the main factor responsible for the substituent chemical shifts, in cases



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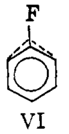

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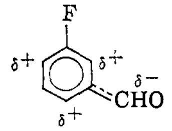

VII

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(10) E. Berliner and E. A. Blommers, *J. Am. Chem. Soc.*, 73, 2481 (1951); 82, 6427 (1960).

where there is no mutual conjugation between substituent and fluorine, is electrostatic polarization of the electrons of the C–F σ bond.[11] The extent of this polarization will depend on the *vector* field along the C–F bond, so that the effect of a charge at some position in the molecule will depend not only on its distance from the C–F bond, but also on its relative direction. Consequently charges at the carbon atom adjacent to fluorine will now have a clear advantage over those at the *ortho* positions (see VI).

Now a significant part of the effect of electromeric substituents in the *meta* position in benzene probably arises from secondary mesomeric field effects.[4] Thus in the case of benzaldehyde, conjugation of carbonyl with the ring, or polarization of the π electrons by a π-inductive effect, will tend to set up positive charges at the positions *ortho* and *para* to carbonyl (VII). The electrostatic field produced by these at a reaction center *meta* to carbonyl will reinforce its $+F$ effect and so make its σ_m constant more positive.

Now the arguments we have presented suggest that this mesomeric-field contribution should be less in the case of fluorine chemical shifts than it is for other chemical and physical properties of side chains; the chemical shift for *m*-fluorobenzaldehyde should therefore be less than one would anticipate from the σ_m constant for formyl, derived from measurements of other properties (*e.g.*, the pK of *m*-formylbenzoic acid). Furthermore, any π charges in the position *meta* to formyl will have a disproportionately large effect in the case of the nmr results. Such charges have been largely ignored in the past since the Hückel method predicts them to be small; this, however, is not the case for more refined treatments. For example, Figure 2 shows π charges calculated by a recently developed SCF–MO procedure;[12] it will be seen that the charges in the positions *meta* to formyl are quite comparable to those in the *ortho* and *para* positions, and are of opposite sign. Such a negative charge in the *meta* position would be expected to decrease still further the substituent chemical shift in *m*-fluorobenzaldehyde.

The same argument can be applied to $-M$ substituents such as amino; here the π polarization will lead to negative π charges in the positions *ortho* and *para* to the substituent, but positive π charges in the *meta* positions. Substituents of this kind exert a $+F$ effect as shown by the sign of their σ_I constants; the corresponding values of σ_m are often negative because the ($+F$) field effect is outweighed by the mesomeric field contribution. This contribution should again be less for fluorine nmr than for other side-chain properties; the substituent chemical shifts in compounds such as *m*-fluoroaniline should therefore be less negative than one would anticipate from the corresponding values of σ_m.

An obvious corollary of this argument is that electromeric substituents should exert a *greater* effect in the *para* positions of fluorobenzene than one would expect from the corresponding values of σ_p; such is indeed the case.[8] Taft and his collaborators[8] have tried to explain this in terms of mutual conjugation between fluorine and the substituent; however there seems to be no need to postulate an effect of this kind–and it seems in any case unlikely to be significant in the case of $-M$ substituents such as NH_2.

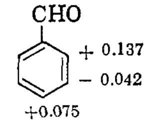

Figure 2. π charges in benzaldehyde, calculated by a SCF–MO procedure.[12]

These arguments incidentally throw doubt on the validity of Taft's treatment of substituent effects in general,[13] and nmr chemical shifts in particular.[8] His analysis is based on the assumption that an electromeric substituent exerts a resonance interaction in the *meta* position of benzene that is some fixed fraction of the effect it produces in the *para* position. Our arguments suggest that the over-all *meta* interaction represents a combination of two distinct contributions: first, a mesomeric field effect which necessarily has the same sign as the mesomeric effect in the position *para* to the substituent; secondly, a true *meta* mesomeric interaction of *opposite* sign. The relative contributions of these may again be much the same for a range of side-chain reactions, simply because the reaction center is in each case at much the same distance from the ring. This consistency does not, however, justify Taft's interpretation of his $(\sigma_m)_R$ constants as representing contributions by true *meta* resonance interactions; indeed, if our arguments are correct, the *meta* resonance interaction should be of *opposite* sign to that assumed by Taft. Moreover his analysis would be expected to break down in cases where the geometry does not conform to the usual pattern; this seems to provide a much simpler explanation of the apparently anomolous behavior of substituent chemical shifts in fluorobenzene than the various *ad hoc* assumptions that Taft was forced to make in order to fit them into his scheme.

A similar complication may arise in other cases with substituents which exert both mesomeric and field effects. Consider for example the group NH_2 which can be classified as $-M$, $+F$. In derivatives of aniline, there will be two distinct effects operating; firstly, a field effect ($+F$) due to the polar C–N σ bond; secondly an opposing mesomeric field effect due to the presence of negative π charges in the positions *ortho*, *para* to NH_2. In a benzene derivative carrying a *m*-amino substituent, the mesomeric effect predominates, for the positions *ortho* to the side chain are much nearer to it than is the C–N dipole, and these positions, being *ortho* and *para* to NH_2, carry negative π charges. The situation will be very different in the case of 4-substituted biphenyls with an amino group in the 3′ position; here the π polarization due to the amino group is confined almost entirely to the adjacent ring—and the atoms in this are all at comparable distances from the side chain. Consequently the relative contribution of the $+F$ effect should be greater than it is in benzene; the effective σ constant of NH_2 in 3′-amino-4-substituted biphenyls should therefore be less negative than one would expect. Similar considerations will of course

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[11] See M. J. S. Dewar, R. C. Fahey, and P. J. Grisdale, *Tetrahedron Letters*, **6**, 343 (1963).

[12] M. J. S. Dewar and G. J. Gleicher, work in course of publication.

[13] See R. W. Taft, *J. Phys. Chem.*, **64**, 1805 (1960).

apply even more forcefully to 4-substituted terphenyls with a 3′′-amino group. The data in Tables I, II, and III certainly seem to support these speculations; thus the substituent chemical shift for 3′-amino-4-fluorobiphenyl is much less than one would expect from the *FM* relation (see Figure 1), and the ratio of substituent chemical shifts for 3′′-amino-4-fluoroterphenyl and 3′-amino-4-fluorobiphenyl is also unexpectedly small (Table IV).

Table IV lists ratios of substituent chemical shifts in 4-fluorobiphenyl and 4-fluoroterphenyl for three electron-withdrawing substituents ($CHBr_3$, CN, and $COOCH_3$); the values in each case are close to 2.5. Now the mesomeric effect is probably small in the case of these compounds, while the arguments in the previous paragraph show that contributions from mesomeric field effects would tend to increase the ratio; the ratio of the long-range nonconjugative effects of substituents in the 3′ position of 4-fluorobiphenyl, and in the 3′′ position of 4-fluoroterphenyl, must therefore be not greater than 2.5. If these long-range interactions were due to a classical inductive effect, brought about by successive polarization of intervening σ bonds, the corresponding fall-off constant (*i.e.*, the attenuation factor per bond) would be 0.7; since such a value is physically impossible and in any case completely at variance with other experimental evidence,[4] our results provide a further strong argument for the thesis that long-range "inductive" interactions are in fact due to a direct field effect.

The ratio is, however, much less than would be expected if the field effect varied inversely with distance. It corresponds closely to the ratio (2.7) that would be expected for an inverse square law. Now the arguments given in part IV[4] for assuming the field effect to vary inversely with distance were based on two considerations: firstly, that the dipoles associated with polar bonds are of finite size; secondly, that most measurements of substituent effects are carried out in polar solvents. In the present case, however, we are dealing with measurements in a relatively nonpolar medium, referring to molecules in which the "reaction center" (*i.e.*, fluorine) is relatively remote from the substituent; in this case the electrostatic field set up by the substituent in the region of the C–F bond could well approximate to that of a point dipole in a medium of uniform dielectric constant, *i.e.*, to an inverse square dependence on distance—as is observed.

Summary and Conclusions

The classical representation of substituent effects is in effect a perturbation treatment, in which the perturbations of an adjacent molecule by a given substituent are represented in terms of the localized bond model.[14] This conventional description is therefore as artificial as the model on which it is based, and any justification must lie in its practical utility rather than its truth. In part IV of this series,[4] it was pointed out that, even within this framework, there are very many different types of possible substituent effects; if all of these had to be invoked, the resulting picture would be so complicated and over-parametrized as to be essentially useless.

There can be no doubt that electromeric substituents, when attached to a conjugated system, can exert a long-range influence on other groups by polarization of the intervening π electrons; this is the so-called mesomeric effect. There is also no doubt[15] that charged substituents can exert long-range effects on other groups by direct electrostatic interactions across space, the so-called field effect. The mesomeric and field effects must therefore be included in any conventional description of substituents. For historic reasons organic chemists have, however, preferred to treat substituents in terms of mesomeric and σ-inductive effects, the field effect being neglected; this is an illogical procedure, for several reasons. First, there is no direct evidence that the σ-inductive effect can be propagated efficiently along a chain of bonds; indeed the available evidence suggests[4] that the fall-off factor is much smaller than has been commonly supposed. Secondly, a large fall-off factor would imply an unreasonably large polarizability of σ electrons, contrary to both experience and theory. Thirdly, whereas there is no direct evidence that the σ-inductive effect can ever be important over long distances, there is clear experimental evidence[15] that the field effect must be important under these conditions. Any two-parameter treatment of substituent effects must therefore be based on a mesomeric–field combination, rather than a mesomeric–σ-inductive one.

Previous papers of this series[2,4] have shown that the effects of substituents can indeed be interpreted with fair success in this way. The main difficulty lies in estimating the variation of the field effect with distance; in the earlier work this was crudely assumed to involve an inverse first-order dependence. The work described here provides general support for this picture, but with two very important provisos.

Firstly, it seems clear that at least two additional effects must be postulated, *i.e.*, the π-inductive and mesomeric field effects. The first of these presents no real problem since it can be shown[4] by a simple perturbational treatment that the π-inductive and mesomeric effects follow a common pattern; both can be described together by a common parameter. The mesomeric field effect, however, is much more troublesome, since the problem of estimating the variation of field effect with distance appears here in an accute form. As a matter of fact it was already apparent in earlier work[4] that some additional effect must be postulated, over and above the mesomeric and field effects, in order to account for the difference between σ_m and σ_I for $-M$ substituents such as OH or NH_2; the mesomeric–field effect seemed a likely candidate.

Secondly, the ratios of substituent chemical shifts for a given substituent in II and III are much closer to that (2.7) calculated for an inverse square dependence on distance than that (1.6) for an inverse first power. This is not surprising, in view of the arguments put forward in part IV, but it emphasizes the difficulties inherent in estimating field effects quantitatively. In part IV it was pointed out that the field effect due to a dipolar substituent should vary approximately as the inverse first power of distance provided that the distance to the reaction center is not much greater than the length of the substituent dipole, and provided that the sur-

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[14] See, *e.g.*, M. J. S. Dewar, "Hyperconjugation," Ronald Press, Inc., New York, N. Y., 1962; *Tetrahedron* **19**, 89 (1964); *Chem. Eng. News*, **43**, 86 (1965).

[15] J. G. Kirkwood and F. H. Westheimer, *J. Chem. Phys.*, **6**, 506 (1938); F. H. Westheimer and J. G. Kirkwood, *ibid.*, **6**, 513, (1938).

rounding medium is a highly polar solvent. The measurements reported here meet neither of these conditions. The distances from substituent to fluorine were large, particularly in the case of III, and the fluorine nmr spectra were measured in aprotic solvents.

One final point that has emerged from these studies is the apparent suitability of fluorine nmr chemical shifts as a measure of long-range field effects. We hope to obtain further evidence concerning the variation of the field effect with distance, and the effect of changing the solvent, by studying the nmr spectra of saturated fluorides containing suitable substituents at various distances from fluorine.

Experimental Section

4-Fluoro-4′-iodobiphenyl. Iodination of 4-fluorobiphenyl[16] (15.3 g) by the method of Wirth, *et al.*,[17] gave 4-fluoro-4′-iodobiphenyl (23.0 g, 87%) as colorless cubes (from ethanol), mp 89.5–90.5°.

Anal. Calcd for $C_{12}H_8FI$: C, 48.34; H, 2.71; I, 42.57; F, 6.37. Found: C, 48.14; H, 2.44; I, 42.36; F, 6.13.

The structure of this material was indicated by its conversion of 4′-fluorobiphenyl-4-carboxylic acid (see below).

4′-Fluorobiphenyl-4-carboxylic Acid. A Grignard reagent prepared from 4-fluoro-4′-iodobiphenyl (5 g) and magnesium (0.5 g) in anhydrous ether (100 ml) was poured onto Dry Ice, and the resulting mixture was allowed to stand at room temperature until the excess Dry Ice had evaporated. Suitable work-up afforded 4-fluorobiphenyl-4′-carboxylic acid (3.15 g, 87%) as white feathers (from ethanol–water), mp 236–237°.

Anal. Calcd for $C_{13}H_9FO_2$: C, 72.22; H, 4.20; F, 8.79. Found: C, 72.20; H, 4.31; F, 8.54.

Identical material (mixture melting point and infrared spectrum) was obtained by carbonation of the Grignard reagent obtained from a commercial sample of 4-fluoro-4′-bromobiphenyl.

Methyl 4′-Fluorobiphenyl-4-carboxylate. 4′-Fluorobiphenyl-4-carboxylic acid (500 mg) was esterified by refluxing overnight with absolute methanol (50 ml) and concentrated sulfuric acid (1 ml). The methyl ester (150 mg) was obtained as colorless plates (from ethanol–water), mp 98.5–99.5°.

Anal. Calcd for $C_{14}H_{11}FO_2$: C, 73.03; H, 4.82; F, 8.25. Found: C, 73.10; H, 4.94; F, 8.21.

4-Fluoro-4′-cyanobiphenyl. A mixture of 4-fluoro-4′-iodobiphenyl (5.0 g), cuprous cyanide (2 g), and anhydrous pyridine (5 ml) was heated under reflux with stirring at 225–230° for 27.5 hr in a 50-ml flask, giving 4-fluoro-4′-cyanobiphenyl (2.27 g, 68%) as colorless needles (from ethanol–water), mp 116–117°.

Anal. Calcd for $C_{13}H_8NF$: C, 79.17; H, 4.09; N, 7.10; F, 9.63; mol wt, 197. Found: C, 79.35; H, 4.29; N, 6.85; F, 9.65; mol wt (mass spectrum), 197.

4-Fluoro-4′-acetamidobiphenyl. Degreased 40-mesh iron filings (5 g) were added to a solution of 4-fluoro-4′-nitrobiphenyl (2 g) in refluxing glacial acetic acid (50 ml) and refluxing continued for 20 hr. The mixture, after cooling and treatment with sodium carbonate solution followed by ether extraction, afforded 4-fluoro-4′-acetamidobiphenyl (1.5 g, 71%) as microscopic colorless crystals (from ethanol–water), mp 205.5–206.5° (lit.[17] mp 205–205.5°).[18]

4-Amino-4′-fluorobiphenyl. Reductive acetylation of commercial 4-fluoro-4′-nitrobiphenyl gave 4-acetamido-4′-fluorobiphenyl, mp 205.5–206.5° (lit.[18] mp 205–205.5°), converted by hydrolysis to 4-amino-4′-fluorobiphenyl, mp 121.5–122° (lit.[19] mp 120°).

3-Nitro-4′-fluorobiphenyl. A. This compound was obtained in very low yield by an Ullmann reaction, by heating a stirred mixture of *p*-fluoroiodobenzene (6.7 g), *m*-iodonitrobenzene (2.5 g), and copper powder (Venus natural copper fine, No. 44-F, 3.2 g) for 5 hr at 200°. Chromatography from benzene–petroleum ether on alumina gave 3-nitro-4′-fluorobiphenyl as white feathers (from ethanol), mp 88.5–90°.

Anal. Calcd for $C_{12}H_8FNO_2$: C, 66.48; H, 3.70; F, 8.72; N, 6.43. Found: C, 66.62; H, 4.00; F, 8.90; N, 6.43. The ultraviolet spectrum in methylcyclohexane showed a single peak, λ_{max} 248 mμ (ϵ 1.9 $\times$ 10^4).

B. An alternative and more satisfactory synthesis involved acetylation[20] of 3-nitrobiphenyl to 3-nitro-4′-acetylbiphenyl, conversion of this by a Schmidt reaction, followed by hydrolysis, to 3-nitro-4′-aminobiphenyl, mp 125.5–128.5° (lit.[21] mp 127–128°), in 34% over-all yield, followed by diazotization and thermal decomposition of the diazonium fluoroborate, giving 3-nitro-4′-fluorobiphenyl (38%), identical (mixture melting point and infrared spectrum) with the product obtained above.

3-Acetamido-4′-fluorobiphenyl. Reductive acetylation of 3-nitro-4′-fluorobiphenyl (2 g) gave 3-acetamido-4′-fluorobiphenyl (1.55 g, 73.5%) as colorless platelets (from aqueous ethanol), mp 146.5–147°.

Anal. Calcd for $C_{14}H_{12}FNO$: C, 73.35; H, 5.28; F, 8.29; N, 6.11. Found: C, 73.29; H, 5.47; F, 8.28; N, 5.93.

3-Amino-4′-fluorobiphenyl. Hydrolysis of the acetamido compound gave an almost quantitative yield of the amine which crystallized from aqueous alcohol in white platelets, mp 58.0–58.5°.

Anal. Calcd for $C_{12}H_{10}FN$: C, 76.99; H, 5.38; F, 10.15; N, 7.48. Found: C, 77.19; H, 5.37; F, 10.24; N, 7.43.

3-Methyl-4′-fluorobiphenyl. To a stirred refluxing ethereal solution of a Grignard reagent prepared in the usual manner from *p*-fluoroiodobenzene (119.1 g) was added dropwise a benzene solution of 3-methylcyclohexanone (65 g, excess).[22] The product (carbinol) was isolated by ether extraction, and was dehydrated by refluxing overnight with excess 20% aqueous oxalic acid solution. The resulting mixture of isomeric cyclohexenes (71 g, 70% over-all, based on *p*-fluoroiodobenzene) was purified by distillation.

Anal. Calcd for $C_{13}H_{15}F$: mol wt, 190. Found: mol wt (mass spectrum), 190.

The resulting material (71 g) was then heated at 250–260° for 30 min with the theoretical amount (24.0 g) of elemental sulfur. Distillation of the crude product afforded 3-methyl-4′-fluorobiphenyl (44 g, 44% over-all yield, based on *p*-fluoroiodobenzene), $n^{24.5}\mathrm{D}$ 1.5730, bp 80° (0.3 mm).

Anal. Calcd for $C_{13}H_{11}F$: C, 83.84; H, 5.95; F, 10.20; mol wt, 186. Found: C, 83.47; H, 5.83; F, 10.10; mol wt (mass spectrum), 186.

3-Dibromomethyl-4′-fluorobiphenyl. A solution of N-bromosuccinimide (28.5 g), 3-methyl-4′-fluorobiphenyl (12.5 g), and a little benzoyl peroxide, in carbon tetrachloride (250 ml), was boiled for 6 hr under reflux while irradiated with a 150-w tungsten-filament lamp in an aluminum reflector. After cooling and filtering, the solution was distilled under reduced pressure, giving 3-dibromomethyl-4′-fluorobiphenyl as a colorless liquid, bp 171–172° (1.0 mm), which solidified and then crystallized from ethanol in white needles (12.2 g, 53%), mp 97.5–98.5°.

Anal. Calcd for $C_{13}H_9FBr$: C, 45.38; H, 2.64; F, 5.52; Br, 46.46. Found: C, 45.58; H, 2.69; F, 5.37; Br, 46.76.

The proton nmr spectrum of a 13% (w/w) solution in carbon tetrachloride showed a sharp singlet at τ 3.38, area 1 ($\mathrm{ArC}\mathit{H}\mathrm{Br}_2$), and a multiplet extending from 2.33 to 3.06, area 8 (aromatic protons). Peaks in the multiplet occurred at the following τ values: 2.33, 2.35, 2.45, 2.51, 2.58, 2.78, 2.91, 3.06.

4′-Fluorobiphenyl-3-carboxaldehyde. 3-Dibromomethyl-4′-fluorobiphenyl, prepared as above from 3-methyl-4′-fluorobiphenyl (50 g), was hydrolyzed to the carboxaldehyde by boiling an aqueous alcoholic solution overnight in the presence of freshly precipitated calcium carbonate. The oily product was distilled under reduced pressure, giving 4-fluorobiphenyl-3′-carboxaldehyde as a colorless oil (41.3 g, 77%), bp 114–116° (0.7 mm), $n^{23}\mathrm{D}$ 1.5659.

Anal. Calcd for $C_{13}H_9FO$: mol wt, 200. Found: mol wt (mass spectrum), 200.

Evidence for the structure of the carboxaldehyde was provided by its conversion to 3-cyano-4′-fluorobiphenyl and to 4-fluorobiphenyl-3′-carboxylic acid (described below). The carboxylic acid thus prepared gave an undepressed mixture melting point with an authentic sample, and gave an infrared spectrum which was identical in all respects with that of the authentic sample.

4′-Fluorobiphenyl-3-carboxylic Acid. A. An unambiguous synthesis was effected by heating 3-dibromomethyl-4′-fluorobiphenyl (5 g) with selenium dioxide (1.65 g) at 160–170° for 10 min. The acid was obtained as colorless feathers from aqueous ethanol (0.4 g, 13%), mp 186–187°.

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(20) E. Berliner and E. A. Blommers, *J. Am. Chem. Soc.*, **73**, 2479 (1951).

(21) F. H. Case, *ibid.*, **61**, 767 (1939).

(22) (a) R. J. Arnold, C. Collins, and W. Zenk, *ibid.*, **62**, 1983 (1940); (b) I. R. Sherwood, W. F. Short and R. Stansfield, *J. Chem. Soc.*, 1832 (1932).

Anal. Calcd for $C_{13}H_9FO_2$: C, 72.22; H, 4.20; F, 8.79; mol wt, 216. Found: C, 72.10; H, 4.35; F, 8.62, 8.89; mol wt (mass spectrum), 216.

B. 4-Fluorobiphenyl-3-carboxylic acid was also prepared in 79% yield by permanganate oxidation[23] of the corresponding aldehyde.

Methyl 4′-Fluorobiphenyl-3-carboxylate. Esterification of 3′-carboxylic acid (7.8 g), followed by fractional distillation through a 24-in. spinning-band column, gave methyl 4′-fluorobiphenyl-3-carboxylate as a colorless oil (5.85 g, 70%), bp 129–132° (0.6 mm), $n^{26.5}\text{D}$ 1.5784.

Anal. Calcd for $C_{14}H_{11}FO_2$: C, 73.03; H, 4.82; F, 8.25; mol wt, 230. Found: C, 73.20; H, 4.74; F, 8.31, 8.54; mol wt (mass spectrum), 230.

3-Cyano-4′-fluorobiphenyl. 4-Fluoro-3′-biphenylcarboxaldoxime, prepared from the corresponding aldehyde,[24] was dehydrated by refluxing with acetic anhydride (40 ml).[25] Fractional distillation of the product through a 24-in. spinning-band column gave 3-cyano-4′-fluorobiphenyl (6 g) as a colorless oil, bp 122° (0.6 mm), which solidified and after crystallization from ethanol had mp 64.5–65°.

Anal. Calcd for $C_{13}H_8FN$: C, 79.17; H, 4.09; F, 9.63; N, 7.10; mol wt, 197. Found: C, 79.51; H, 4.23; F, 9.99; N, 7.10; mol wt (mass spectrum), 197.

3-(*p*-Fluorophenyl)cyclohex-2-en-3-one. An ethereal solution of 3-ethoxycyclohex-2-en-1-one[26] (14.0 g) was added dropwise to a boiling ethereal Grignard reagent prepared from *p*-bromofluorobenzene (26.3 g). Volatile material was then steam distilled and the residue was extracted with ether and fractionated, giving a mixture of isomers of 3-(*p*-fluorophenyl)cyclohexen-1-one as a pale yellow oil (14.0 g, 73.7%), bp 138–140° (0.8 mm), $n^{26}\text{D}$ 1.5879, which solidified on standing but melted over a wide temperature range up to 45°.

Anal. Calcd for $C_{12}H_{11}FO$: mol wt, 190. Found: mol wt (mass spectrum), 190.

The corresponding azine crystallized from benzene–ethanol as a yellow powder, mp 189–189.5°.

Anal. Calcd for $C_{24}H_{22}N_2F_2$: C, 76.57; H, 5.89; F, 10.09; N, 7.44. Found: C, 76.36; H, 5.76; F, 10.15; N, 7.65.

3-Hydroxy-4′-fluorobiphenyl. The above cyclohexenone (5 g) was aromatized[27] giving 3-hydroxy-4′-fluorobiphenyl which after sublimation formed colorless needles (2.60 g, 53%), mp 77–79°.

Anal. Calcd for $C_{12}H_9FO$: C, 76.58; H, 4.82; F, 10.10; mol wt, 188. Found: C, 76.58; H, 4.97; F, 10.27; mol wt (mass spectrum), 188.

3-Methoxy-4′-fluorobiphenyl. The corresponding phenol (13.3 g) was methylated with dimethyl sulfate (9.5 g) and distilled, giving 3-methoxy-4′-fluorobiphenyl as a colorless oil, bp 94° (0.6 mm), $n^{22}\text{D}$ 1.5820.

Anal. Calcd for $C_{13}H_{11}FO$: C, 77.21; H, 5.48; F, 9.40; mol wt, 202. Found: C, 77.47; H, 5.53; F, 9.18; mol wt (mass spectrum), 202.

3-Bromo-4′-fluorobiphenyl. 3-Bromo-4′-acetamidobiphenyl was prepared from 3-bromobiphenyl by the same sequence of reactions as that used for 3-nitro-4′-acetamidobiphenyl (procedure B). The acetamido compound was obtained in 43% over-all yield as colorless needles (from aqueous ethanol), mp 181–183° (lit.[28] mp 182–183°).

Anal. Calcd for $C_{14}H_{12}BrNO$: C, 57.95; H, 4.17; Br, 27.54; N, 4.82. Found: C, 58.30; H, 4.46; Br, 27.65; N, 4.73.

Hydrolysis to the amine, diazotization, and treatment with fluoroboric acid gave 3-bromobiphenyl-4-diazonium fluoroborate, mp 101–109° dec, in 95% over-all yield. Decomposition of dry salt (38.5 g) in portions in mineral oil at 170°, followed by steam distillation, gave 3-bromo-4′-fluorobiphenyl as a colorless oil (20.2 g, 77.5%), bp 103–105° (0.6 mm), $n^{23}\text{D}$ 1.5370.

Anal. Calcd for $C_{12}H_8BrF$: mol wt, 251. Found: mol wt, (mass spectrum), 250, 252.

The structure of this material was confirmed by conversion to 3-cyano-4′-fluorobiphenyl by the method used above for the 4,4′ isomer; the product was identical (mixture melting point and infrared spectrum) with authentic material (see above).

1-(4′-Fluoro-4-biphenyl)cyclohex-1-ene. Treatment of a Grignard reagent from 4-fluoro-4-iodobiphenyl (5 g) with cyclohexanone (2 g) in benzene (25 ml), following the procedure used to make 3-(*p*-fluorophenyl)cyclohex-2-en-3-one, gave 1-(4′-fluoro-4-biphenyl)-cyclohex-1-ene (3.2 g, 75%) as a colorless microcrystalline solid, mp 159–160.5° (from ethanol).

Anal. Calcd for $C_{18}H_{17}F$: C, 85.68; H, 6.79; F, 7.53; mol wt, 252. Found: C, 85.32; H, 6.72; F, 7.62; mol wt (mass spectrum), 252.

4-Fluoroterphenyl. Aromatization of the cyclohexene compound (9.3 g) by boiling with chloranil (Eastman practical grade, 18.7 g) in xylene (65 ml) for 14 hr gave 4-fluoroterphenyl (2.1 g, 23%) as silver plates (from benzene–ethanol), mp 216–217°.

Anal. Calcd for $C_{18}H_{13}F$: C, 87.07; H, 5.28; F, 7.65; mol wt, 248. Found: C, 87.22; H, 5.29; F, 7.55; mol wt (mass spectrum), 248.

3-Methyl-4′′-fluoroterphenyl. A Grignard reagent from 4-fluoro-4′-iodobiphenyl (20.6 g) was treated as before with 3-methylcyclohexanone (8 g), giving the expected mixture of isomeric cyclohexenes (16.0 g) as an amorphous, white solid (from ethanol), mp 125–126.5°.

Anal. Calcd for $C_{19}H_{19}F$: mol wt, 266. Found: mol wt (mass spectrum), 266.

The mixture of cyclohexenes (2.2 g) was aromatized by heating with the theoretical amount of elemental sulfur at 250–260° for 15 min, giving 3-methyl-4′′-fluoroterphenyl (1.1 g, 51%) as a colorless powder (from benzene–ethanol), mp 150–150.5°.

Anal. Calcd for $C_{19}H_{15}F$: C, 86.99; H, 5.76; F, 7.24; mol wt, 262. Found: C, 86.71; H, 5.70; F, 7.47; mol wt (mass spectrum), 262.

3-Dibromomethyl-4′′-fluoroterphenyl. Bromination of 3-methyl-4′′-fluoroterphenyl (2.0 g) with N-bromosuccinimide (3.4 g), following the procedure used for 3-dibromomethyl-4-fluorobiphenyl, gave 3-dibromomethyl-4′′-fluoroterphenyl (2.15 g, 67%) as lustrous white plates (from aqueous ethanol), mp 129.5–130.5°.

Anal. Calcd for $C_{19}H_{13}FBr$: C, 54.32; H, 3.12; Br, 38.04; F, 4.52. Found: C, 54.51; H, 3.02; Br, 37.82; F, 4.35.

The proton nmr spectrum of a 20% (w/w) solution in chloroform-*d* showed a sharp singlet at τ 3.30, area 1 ($ArCHBr_2$), an A_2B_2 pattern at 2.66 and 2.96 with J_{AB} = 9 cps, corresponding to the protons on the central ring, and a complex multiplet from τ 2.20 to 2.54 due to the remaining aromatic protons. The total integrated area for all the aromatic protons was 12.

An attempt to brominate 3-methyl-4′′-fluoroterphenyl with bromine in carbon tetrachloride in presence of light evidently led to ring bromination, since the product had a molecular weight corresponding to a monobromo derivative, but was shown by its proton nmr spectrum to have retained the methyl group intact.

3-Nitro-4′-iodobiphenyl. Iodination[17] of 3-nitrobiphenyl (17.9 g) gave 3-nitro-4′-iodobiphenyl (20.8 g, 71.3%) which crystallized from benzene–petroleum ether in long, colorless needles, mp 115.5–116.5°.

Anal. Calcd for $C_{12}H_8INO_2$: C, 44.33; H, 2.48; I, 39.04; N, 4.31. Found: C, 44.53; H, 2.41; I, 39.30; N, 4.28.

The structure followed from the ultraviolet spectrum which showed peaks at 327 mμ (log ϵ 4.24) and 229 mμ (log ϵ 3.75), characteristic of an unhindered biphenyl. This excluded the only alternative structure (3-nitro-2′-iodobiphenyl) allowed by analogy and theoretical considerations.

Attempts to Prepare 3-Nitro-4′′-fluoroterphenyl. Numerous attempts to prepare 3-nitro-4′′-fluoroterphenyl by Ullmann reactions from 4-iodo-4′-fluorobiphenyl and *m*-bromo- or *m*-iodonitrobenzene gave only the symmetrical coupling products, 3,3′-dinitrobiphenyl and 4,4′′′-difluoroquaterphenyl. The latter compound, which has not been reported previously, crystallized from benzene in white flakes, mp 316.5–317°.

Anal. Calcd for $C_{24}H_{16}F_2$: C, 84.19; H, 4.71; F, 11.10. Found: C, 83.92; H, 4.74; F, 11.46.

In one experiment a further product of unknown structure was isolated; it crystallized from benzene–ethanol in colorless plates, mp 178–178.5°.

Anal. Calcd for $C_{24}H_{16}F_2O_2$: C, 77.00; H, 4.31; F, 10.15; N, 0.00; mol wt, 374. Found: C, 77.34; 77.18; H, 4.44, 4.47; F, 9.78, 10.19; N, 0.00; mol wt (mass spectrum), 374.

Attempts to condense *p*-fluoroiodobenzene with 3-nitro-4′-fluorobiphenyl also gave only the symmetrical coupling products, 4,4′-difluorobiphenyl and 3,3′′′-dinitroquaterphenyl. The latter, also a new compound, separated from benzene–ethanol as a pale yellow powder, mp 211–210°.

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Anal. Calcd for $C_{24}H_{16}N_2O_4$: C, 72.72; H, 4.07; N, 7.07. Found: C, 72.96; H, 4.15; N, 7.27, 7.45.

3-(4′-Fluoro-4-biphenylyl)cyclohex-2-en-1-one. Prepared from 4-fluoro-4′-iodobiphenyl (16.0 g) by the method used for 3-(*p*-fluorophenyl)cyclohex-2-en-1-one, the ketone was obtained as an amorphous, yellow powder which resisted purification. It was characterized as the azine which separated from xylene as a bright lemon-yellow powder, mp 270.5–271°.

Anal. Calcd for $C_{36}H_{30}F_2N_2$: C, 81.79; H, 5.72; F, 7.19; N, 5.30. Found: C, 81.56; H, 5.88; F, 7.31; N, 5.55.

3-Amino-4′′-fluoroterphenyl. The above azine (0.55 g) was boiled under reflux with 10% palladized charcoal (0.30 g) in triglyme (35 ml) for 42 hr, then filtered and poured into water. The precipitate was collected and sublimed under vacuum. The sublimate of 3-amino-4′′-fluoroterphenyl (0.23 g, 42%) after crystallization from ethanol had mp 194–195°.

Anal. Calcd for $C_{18}H_{14}FN$: C, 82.11; H, 5.36; F, 7.22; N, 5.32; mol wt, 263. Found: C, 81.69; H, 5.18; F, 7.35; N, 5.48; mol wt (mass spectrum), 263.

3-Cyano-4′′-fluoroterphenyl. Dehydration of *m*-iodobenzamide (24.7 g) with thionyl chloride[29] gave *m*-iodobenzonitrile (18.4 g, 80%) as a colorless oil, bp 77° (0.3 mm), which solidified on standing, mp 39.5–41° (lit.[30] mp 41°). A mixture of *m*-iodobenzonitrile (10 g), 4-fluoro-4′-iodobiphenyl (18 g), and copper powder (30 g, Metals Desintegrating Corp., Elizabeth, N. J.) was heated for 23 hr at 200–215°. The product was extracted with xylene in a Soxhlet and the extract cooled to 0° and filtered to remove 4,4′′′-difluoroquaterphenyl (3.5 g), mp and mmp 316.5–317°. The filtrate was concentrated and chromatographed on alumina, using gradient elution with benzene–ligroin (Skelly B). 3-Cyano-4′′-fluoroterphenyl was eluted first; after crystallization from ethanol and sublimation it formed colorless plates (3.3 g, 28%), mp 110.5–111.5°.

Anal. Calcd for $C_{19}H_{12}FN$: C, 83.50; H, 4.43; N, 5.13; mol wt, 273. Found: C, 83.30; H, 4.34; N, 5.17; mol wt (mass spectrum), 273.

Further elution gave 3,3′-dicyanobiphenyl which after repeated recrystallization from ethanol followed by sublimation was obtained as a colorless powder (1.0 g, 11.2%), mp 205–205.5°.

Anal. Calcd for $C_{14}H_8N$: C, 82.33; H, 3.95; N, 13.72; mol wt, 204. Found: C, 82.50; H, 4.04; N, 13.67; mol wt (mass spectrum), 204.

Methyl 4′′-Fluorobiphenyl-3-carboxylate. A mixture of methyl *m*-iodobenzoate (10 g), 4-fluoro-4′-iodobiphenyl (17.1 g), and copper powder (30 g) was heated for 23 hr at 190–200°. The product was worked up in the same way as the analogous nitrile, using benzene–pentane for the gradient elution. Methyl 4′′-fluorobiphenyl-3-carboxylate (4.9 g, 44%) crystallized from ethanol in colorless needles, mp 138.5–140°.

Anal. Calcd for $C_{19}H_{15}FO_2$: C, 78.42; H, 4.94; F, 6.20; mol wt, 306. Found: C, 78.24; H, 4.75; F, 6.26; mol wt (mass spectrum), 306.

4,4′′′-Difluoroquaterphenyl (2.0 g) was the only isolable byproduct.

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(29) J. A. Krynitsky and H. W. Carhart, "Organic Syntheses," Coll. Vol. 4, John Wiley and Sons, Inc., New York, N. Y., 1963, p 436.

(30) P. Griess, *Ber.*, 2, 369 (1869).

Conformational Analysis. XI. Configurational Equilibria and Chromic Acid Oxidation Rates of Alkylcyclohexanols. Deformation Effects[1]

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Abstract: Results of Raney nickel and aluminum alkoxide catalyzed epimerizations of various alkylcyclohexanols are compared. The two methods agree in solvent isopropyl alcohol. In benzene the equilibria are somewhat displaced toward the axial alcohols. The *cis–trans* equilibria of 3- and 4-methyl-, ethyl-, and isopropylcyclohexanols are consistent with those of the (conformationally homogeneous) 3- and 4-*t*-butylcyclohexanols making the assumption that in each separate series the conformational energies of alkyl and hydroxyl are additive. The configurational equilibrium positions are different in the 2-, 3- and 4-alkylcyclohexanol series. The results in the 2 series are explained assuming that the cyclohexane ring is flattened, which leads to a greater *gauche* interaction of *cis* (e,a) substituents as compared to *trans* (e,e). In the case of 2-ethyl- and 2-isopropylcyclohexanol, there is also involved a steric interaction of certain rotational conformations of the alkyl substituent with the equatorial hydroxyl group of the *trans* isomer. Results in the 3 series are tentatively explained by eclipsing of the alkyl group at C_3 with hydrogen at C_2 when the hydroxyl group at C_1 is axial. Only hydrogen–hydrogen eclipsing is involved in the 4 series. This interpretation is supported by a study of the chromic acid oxidation rates of the various alkylcyclohexanols.

In a previous publication[3] we have compared the results of Raney nickel catalyzed equilibration of the epimeric 4-*t*-butylcyclohexanols, 3,5-dimethylcyclohexanols, and 3,3,5-trimethylcyclohexanols with previously available data on *cis–trans* equilibria established with aluminum isopropoxide. It was concluded[3] that, when the solvent is the same (isopropyl alcohol), the equilibrium mixtures produced by the two reagents are the same, as they should be, and the the equilibrium is solvent dependent, being more on the side of the alcohol with equatorial hydroxyl in hydrogen-donating solvents than in aprotic solvents.

In the present work we have extended the Raney nickel and aluminum alkoxide catalyzed *cis–trans* equilibrations to other conformationally homogeneous 3-alkyl- and 3,5-dialkyl-substituted cyclohexanols as well as to some conformationally heterogeneous 2-, 3-, and 4-alkylcyclohexanols. The results are sum-

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[1] Paper X: E. L. Eliel and T. J. Brett, *J. Am. Chem. Soc.*, 87, 5039 (1965).

[2] The Radiation Laboratory is operated under contract with the Atomic Energy Commission. This is AEC Document No. COO-38-436.

[3] E. L. Eliel and S. H. Schroeter, *J. Am. Chem. Soc.*, 87, 5031 (1965).