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^{13}C and ^{19}F NMR Spectra of Substituted Ethyl α-Fluorocinnamates. Application of the DSP-NLR Equation.

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Abstract

^{13}C and ^{19}F NMR spectra of 12 *p*-substituted and 9 *m*-substituted ethyl α-fluorocinnamates, along with that of the parent compound, have been recorded and analyzed by DSP and DSP-NLR equations. ε values found for the correlation of chemical shifts of both the β-carbon atom of the styrene skeleton and the F atom show near additivity of the effect of individual substituents on C4 shifts in *p*-disubstituted benzenes. Despite this, correlations using the DSP-NLR equation are not greatly improved over those of the DSP equation, either for sites showing excellent or poor correlations. Also, the magnitude of the ε values appropriate for different sites on the side chain show no significant relationship to the percentage of the sensitivity at the site attributed to resonance interaction. Consequently, the utility of the DSP-NLR method seems limited. Substituent effects at F are normal, in contrast to the expectation based on charge alternation that they would be inverse. CNDO/2 charge densities calculated for representative methyl α-fluorocinnamates reveal that π densities at both F and the β-carbon atom of the styrene skeleton accord with normal substituent effects.

Introduction

The use of dual substituent parameter equations has led to the proposal of several substituent scales designed to separate resonance and inductive/field effects. Ehrenson, Brownlee, and Taft[1] proposed four different resonance scales, denoted $\sigma_{R(BA)}$, σ_{R^o}, σ_{R^+}, and σ_{R^-}, to accommodate differing situations in which substituents interact mesomerically with the reaction center. Application of these scales, however, has seemed arbitrary, since it is not possible, *a priori*, to predict which scale would provide the best correlation in every instance. Consequently, because the resonance effect of a given substituent seems to depend upon the demands placed upon the substituent by the reaction center, several different quantitative approaches to treating non-linear resonance demands have been developed.[2-7] None of these approaches, however, has been subjected to extensive experimental scrutiny.

Eq 1 represents one such approach.[7] In this expression, referred to as the DSP-NLR equation, $\bar{\sigma}_R$, the resonance

$$P_X \quad = \quad \rho_I\sigma_{I,X} \quad + \quad \rho_R\bar{\sigma}_{R,X} \quad + \quad P_H \qquad (1)$$

parameter, is allowed to vary depending upon the nature of the reaction. The property of the substituted compound in question, P_X, is then related to the inductive/field parameter, $\sigma_{I,X}$, the resonance parameter, $\bar{\sigma}_{R,X}$, and the property of the unsubstituted compound, P_H, by means of the sensitivity factors, ρ_I and ρ_R. Further, ε is introduced as an electron demand parameter, such that a particular resonance scale, $\bar{\sigma}_R$, can be generated for each individual reaction or measurement according to eq 2. In the ^{13}C NMR spectra of *p*-X,Y-disubstituted benzenes, in which Y represents a common group within the series and X is a variable substituent, it was found that the σ_R scale did indeed vary in a generally suitable way with the

$$\bar{\sigma}_{R,X} = \sigma_{R^o,X}/(1 - \varepsilon\sigma_{R^o,X}) \qquad (2)$$

electron demand parameter imposed by the common group, Y. Consequently, it was envisioned that the σ_R scale appropriate could be obtained from the σ_{R^o} scale and could lie anywhere between the limiting $\sigma_R{}^+$ and $\sigma_R{}^-$ scales. Based on this approach, ε values were reported for a variety of common groups attached to a benzene ring. Although the DSP-NLR treatment can be criticized because it introduces an additional, apparently disposable, parameter,[8] it does hold the prospect of refining the determination of resonance effects if some consistency of interpretation can be found for the ε values of different groups in various situations. Accordingly, a comparison of ε values reported from *p*-disubstituted benzenes with analogous values derived from β-substituted styrenes, in which substituents are vinylogous to those of the *p*-disubstituted benzenes, is desirable.

A substantial body of ^{13}C NMR shift data for substituted styrenes now exists.[9-16] The chemical shifts of the β-carbon atoms have been analyzed by means of a variety of substituent constants.[14] De and coworkers[16] included a DSP-NLR treatment for several series. More recently, Exner and Budesinsky have applied principal component analysis to several of these data and have found improved statistical correlations.[8] None the less, substituent effects continue to be discussed in terms of a combination of resonance and inductive/field effects and skepticism persists that a universally applicable set of parameters for a dual parameter equation can be found.[8,17] With these compounds, substituent-induced polarization of both the σ- and π-framework results in alternate normal and inverse substituent effects on side-chain atoms.[10] Unfortunately, most series studied to date have contained β-substituents that are electron-withdrawing by both resonance and induction. Thus, the study of some series incorporating β-substituents with other electronic capabilities seemed worthwhile. As part of such a program, we have prepared a series of ethyl *p*-R-α-fluorocinnamates, measured substituent effects at carbon and fluorine using chemical shifts in the NMR spectrum, calculated electron demand parameters, and compared them to the ε values established for side chains in previously reported series.[14] The results of this study are reported here.

Experimental

Compounds **1 a-v** were employed. They were prepared by the procedure of either Elkik[18-22] or Bergmann and Shahak.[23] Each was subjected to a complete spectral characterization, including the recording of ^1H, ^{13}C, and ^{19}F NMR spectra, infrared spectra, and mass fragmentation patterns. In all cases, data accorded completely with structure. A complete analysis of the mass fragmentation patterns has been presented.[24]

Infrared spectra were obtained with a Mattson-Polaris FTIR (Nu 10000) spectrophotometer. NMR spectra were recorded from solutions containing ca. 0.5 g solute in 1.5 mL $CDCl_3$. ^{13}C spectra were recorded with a Varian CFT-20 spectrometer with Me_4Si (TMS) as internal standard. Chemical shifts are reported as ppm downfield from the standard. Assignments were made based on comparison with those of previosly reported compounds,[14] relative intensities, coupling constants, and in some cases, coupled and off-resonance decoupled spectra. ^1H and ^{19}F spectra were recorded at 89.55 and 84.25 MHz, resp., with a JEOL FX90Q spectrometer. ^{19}F spectra were recorded both with and without proton decoupling and chemical shifts are reported as ppm upfield from the internal reference, $CFCl_3$. ^{13}C and ^{19}F chemical shifts are collected in Table I.

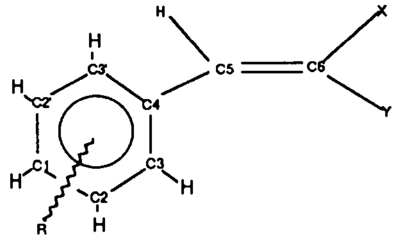
Results and Discussion

DSP and DSP-NLR correlation analyses were done by means of eqs 3 and 4, in which ^{13}C and ^{19}F chemical shifts were correlated with σ_I and σ_{R^o}. The updated substituent constants given by Bromilow, Brownlee, Lopez, and Taft were used.[25]

$$\delta_X = \rho_I\sigma_{I,X} + \rho_R\sigma_{R^o,X} + h \qquad (3)$$

$$\delta_X = \rho_I\sigma_{I,X} + \rho_R\sigma_{R^o,X}/(1 - \varepsilon\sigma_{R^o,X}) + h \qquad (4)$$

Because no substituent constants are available for the phenyl substituent, it was excluded from the analyses. Accordingly, the *p*-substituted series, the results of which are summarized in Table II, was composed of 11 substitutents plus the unsubstituted parent. The *m*-substituted series, summarized in Table III, included 9 substituents and the parent. These tables include the sensitivity factors, ρ_I and ρ_R, the percentage of the sensitivity attributed to resonance interaction as



1 a-v

X = CO_2Et Y = F

R at C1

R
a: $N(Me)_2$
b: OMe
c: OPh
d: Me
e: Ph
f: F
g: Cl
h: Br
i: CO_2Et
j: CF_3
k: CN
l: NO_2

R at C2

R
m: Me
n: OPh
o: OMe
p: F
q: Cl
r: Br
s: CF_3
t: CN
u: NO_2
v: H

TABLE I. Chemical shifts of ethyl α-fluorocinnamates.

	Chemical Shifts									
Compound	C1	C2	C2'	C3	C3'	C4	C5	C6	C7	F
1a	151.10	111.82	111.82	131.95	131.95	119.02	118.37	144.73	162.07	132.37
1b	160.88	114.40	114.40	132.08	132.08	123.96	117.38	146.01	161.61	129.13
1c	158.18	118.31	118.31	132.05	132.05	125.93	116.93	146.42	161.55	127.76
1d	140.06	129.57	129.57	130.32	130.32	128.45	117.61	146.65	161.61	126.89
1e	142.30	127.35	127.35	130.76	130.76	130.19	117.10	147.19	161.34	125.57
1f	163.35	116.03	116.03	132.35	132.35	127.60	116.39	146.97	161.29	126.79
1g	135.64	129.12	129.12	131.48	131.48	129.73	116.21	147.42	161.14	124.82
1h	123.92	132.02	132.02	131.63	131.63	130.10	116.11	147.48	160.88	124.44
1i	130.80	129.93	129.93	130.11	130.11	135.46	116.22	148.21	160.98	122.27
1j	131.34	125.83	125.83	130.48	130.48	134.80	115.83	148.55	161.00	122.35
1k	112.91	132.50	132.50	130.58	130.58	135.56	115.37	148.80	160.62	120.60
1l	147.93	123.98	123.98	130.85	130.85	137.43	114.91	149.07	160.61	120.11
1m	130.58	138.21	128.75	130.99	127.51	130.92	117.69	147.02	161.45	125.96
1n	119.97	157.74	130.07	120.12	125.08	132.80	116.86	147.40	161.16	124.31
1o	115.77	159.82	129.77	115.30	122.96	132.41	117.43	147.22	161.36	125.06
1p	116.68	162.90	130.35	116.79	126.18	133.26	116.22	147.84	161.09	123.46
1q	129.69	134.81	130.04	129.98	128.16	132.98	116.01	147.84	161.00	123.42
1r	132.59	122.85	130.27	132.89	128.69	133.18	115.89	147.75	160.97	123.39
1s	126.41	131.53	129.55	126.94	133.34	132.20	115.95	148.31	161.05	122.94
1t	132.68	113.36	129.83	133.36	134.11	132.51	115.02	148.49	160.65	121.99
1u	124.09	148.59	129.94	124.71	135.64	132.79	114.97	148.65	160.65	121.48
1v	129.71	128.84	128.84	130.33	130.33	131.26	117.51	147.17	161.41	125.54

calculated from eq 5, and the standard statistical measures (the coefficient of determination multiplied by 100 and denoted $100R^2$, the F value, and the standard deviation) for each correlation. In the *p*-substituted series, C4, C6, and F all show excellent correlations according to eq 3, with $100R^2$ values greater than 99, substantial F values, and small standard deviations. The C7 correlation, which is based on a very small range of substituent effects as is typically found for this carbon atom in all series examined to date, is relatively poor ($100R^2$ = 95.01). As expected on the basis of charge alternation, C4 and C6 show normal substituent effects, while C5 and C7 show inverse effects. ^{19}F was expected to show inverse substituent effects, but, in fact, does not. For this series, the electron demand parameter, ε, was also established to the nearest 0.01 using the customary trial and error approach, which is based on minimization of the sum of squared residuals. Calculations were done using both C6 and ^{19}F shifts and good agreement was obtained, also shown in Table II. Interestingly, the $^1J_{FC8}$ coupling constants in the *p*-substituted series ranged from 258.0 Hz for *p*-dimethylamino to 275.2 Hz for *p*-nitro and showed a good correlation (F = 284.4, $100R^2$ = 98.44) with σ_I and σ_R in a dual parameter treatment. The order of increasing value for coupling constants in this series is opposite that found for $^1J_{PC8}$ in *p*-substituted ethyl α-diethylphosphonocinnamates and α-diethylphosphonocinnamonitriles.[26] This is possibly due to the functioning of the P atom as a d_π-p_π acceptor and the F atom as a p_π-p_π donor.

$$\%R = 100[\rho_R/(\rho_I + \rho_R)] \qquad (5)$$

TABLE II. Correlations from eqs 3 and 4 for ethyl *p*-X-α-fluorocinnamates.

Atom	ρ_I	ρ_R	h	%R	$100R^2$	F	SD	ε
C4	5.101	21.338	131.12	80.7	99.59	1083.4	0.33	0.00
C5	-3.249	-2.114	117.32	39.4	98.88	396.7	0.10	0.00
	-3.246	-2.051	117.31	38.7	98.89	399.6	0.10	-0.09
C6	2.138	4.416	147.19	67.4	99.19	550.3	0.11	0.00
	2.109	3.976	147.22	65.3	99.48	860.2	0.09	-0.29
C7	-1.097	-1.197	161.42	52.2	95.01	85.7	0.09	0.00
	-1.080	-0.993	161.40	47.9	95.59	97.5	0.09	-0.48
F	-5.624	-12.990	125.35	69.8	99.01	451.2	0.34	0.00
	-5.564	-12.019	125.26	68.4	99.18	542.4	0.31	-0.22

Correlations given in Table III for *m*-substituted compounds were generally poorer than those for the *p*-substituted series, although the ^{19}F shifts gave an excellent correlation. From principal component analysis, Exner and Budesinsky concluded that the DSP treatment of *m*-substituents represented an over-parameterization.[8] Consequently, analyses of the present data were done using the single substituent parameter equation and σ^{13} values,[14] with the additional values of 0.79 and 0.52 for *m*-phenoxy and *m*-trifluoro, resp., which were determined from previously utilized series. $100R^2$ values for these correlations, also given in Table III, were poorer in all cases except for C6, which showed a modest improvement over the DSP treatment.

TABLE III. Correlations from eq 3 for ethyl *m*-X-α-fluorocinnamates.

Atom	ρ_I	ρ_R	h	%R	$100R^2$	F	SD	SSP[a]
C4	3.262	-1.770	131.02	35.2	92.56	43.6	0.20	30.94
C5	-3.587	-1.990	117.42	35.7	96.65	100.9	0.17	96.43
C6	1.928	1.465	147.24	43.2	97.63	144.2	0.08	98.77
C7	-1.030	-0.544	161.39	34.6	94.19	56.7	0.06	93.30
F	-5.602	-2.690	125.47	32.4	99.74	1329.8	0.07	98.44

[a] $100R^2$ values for correlations using the single substituent parameter equation. See text.

Data from the present study can be used along with previously reported information to obtain a partial assessment of the consistency of interpretation for electron demand parameters. Table IV summarizes the results for *p*-disubstituted benzenes and their vinylogs, as represented by structure 1. This table reveals that, in agreement with the suggestion of De and his coworkers,[16] the effect of vinylogous substituents are very nearly additive if more than one substituent is present on the β-carbon atom of the styrene side chain and that the effect of a single substituent so located is virtually identical to that of the same substituent when attached directly to the benzene nucleus. This is true not only for those substituents that are electron withdrawing by both resonance and inductive/field effects, but also in the case of the strongly mesomerically electron donating fluorine atom. Thus, there seems to be a consistent effect of substituents throughout the various series of compounds.

TABLE IV. Electron demand parameters based on structure 1.

X	Y	ε(Ph-X)[a]	ε(Ph-Y)[a]	ε(calc)[b]	ε[c]
H	H	0.06	0.06	0.12	-0.17[d]
CN	H	-0.60	0.06	-0.54	-0.68
CO-*t*-Bu	H	–	0.06	–	-0.48
CO_2Et	H	-0.48	0.06	-0.42	-0.62
COPh	H	–	0.06	–	-0.58
CN	CN	-0.60	-0.60	-1.20	-1.13
Ph	CN	–	-0.60	–	-0.86
CO_2Et	CN	-0.48	-0.60	-1.08	-1.06
COPh	CN	–	-0.60	–	-1.07
PO_3Et_2	CN	–	-0.60	–	-1.05
COMe	COMe	-0.49	-0.49	-0.98	-0.99
COMe	CO_2Et	-0.49	-0.48	-0.97	-1.06
CO_2Et	CO_2Et	-0.48	-0.48	-0.96	-0.95
PO_3Et_2	CO_2Et	–	-0.48	–	-1.09
CO_2Et	COMe	-0.48	-0.49	-0.97	-1.00
COMe	COPh	-0.49	–	–	-0.89
COPh	$-CH_2CH_2-$	–	0.34	–	-0.68[e]
H	CN	0.06	-0.60	-0.54	-0.70
CO_2Et	F	-0.48	0.14	-0.34	-0.29[f]
CO_2Et	F	-0.48	0.14	-0.34	-0.22[g]

[a] Demand parameters where X or Y is the common group attached directly to a benzene ring bearing a *para* substituent as given in ref. 7. [b] Predicted values based on simple additivity. [c] Unless otherwise noted, values in this column are calculated from the C6 shifts given in ref. 14. [d] Derived from data in ref. 9. [e] Based on *p*-benzylidene derivatives of α-tetralone. [f] From the present data using C6 shifts. [g] From the present data using ^{19}F shifts.

It should be noted, however, that these conclusions are based on series for which the correlations by eq 3 are excellent and that the application of eq 4 produces only a very modest improvement in goodness-of-fit measures. Accordingly, it was of interest to apply this approach to the C5 shifts, for which correlation by means of eq 3 yielded a good, but not excellent, result, and to C7 shifts, which gave a poor correlation with eq 3. These results are also shown in Table II. Two aspects should be noted: first, these correlations are also not significantly improved by the use of eq 4, and second, there seems to be no clear-cut relationship between the sensitivity factors, as expressed by %R from eq 5, and the electron demand parameter appropriate for the various sites in the vinylic side chain. Intuitively, it might have been expected that greater or lesser demand for electron donation or withdrawal through resonance at these different sites might manifest itself in the demand parameter. Thus, the combination of lack of significant improvement in the correlations and the irregularity of ε at the various sites suggests that eq 4 may not have wide-ranging utility.

Variations in π electron densities in model compounds as calculated by the CNDO/2 procedure were used previously[10] to interpret inverse and normal substituent effects and it was of interest to see if such a simple approach could cast light on the seemingly anomolous substituent effect found at the fluorine atom in the present series. Accordingly, calculations were carried out for an abbreviated series of methyl *p*-R-α-fluorocinnamates, using standard geometries and parameters.[27] The results are shown in Table V. The s electron densities on both C6 and F are essentially invariant throughout the series. Both the π densities and the total electron densities on C6 show the general trend expected for normal substituent effects, with *p*-dimethylamino being anomalous and a slight irregularity between *p*-trifluoromethyl and *p*-cyano. The total electron density at F shows only slight variation and no definite trend, but the π density shows the same trend as shown by C6, although the range is smaller. Thus, the calculated variations in π electron density at fluorine agree well with the normal substituent effect exerted at that site, even though charge alternation based on substituent effects would have predicted an inverse effect. Additional work with other heteroatoms in this position will be reported in the future.

TABLE V. Electron densities for *p*-substituted methyl α-fluorocinnamates.[a]

	Atom					
	C6			F		
Subst	s	p	π	s	p	π
$N(Me)_2$	1.0287	2.8125	1.0662	1.8516	5.3752	1.9526
OMe	1.0321	2.8450	1.0897	1.8515	5.3689	1.9543
Me	1.0329	2.8382	1.0806	1.8516	5.3673	1.9535
F	1.0331	2.8363	1.0788	1.8515	5.3675	1.9530
H	1.0332	2.8341	1.0760	1.8516	5.3666	1.9527
CF_3	1.0322	2.7792	1.0239	1.8515	5.3692	1.9478
CN	1.0315	2.7868	1.0336	1.8516	5.3706	1.9486
NO_2	1.0335	2.7969	1.0117	1.8515	5.3675	1.9462

[a] The molecular framework was constrained in the xz plane. The column labelled π refers to the density in the p_y orbital.

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