

water. Yield, 0.490 g. (87%), m.p. 219–220°. $[\alpha]_D^{22} +5.3^\circ$ (c, 1.20 in pyridine). For analysis a sample was dried for 12 hours *in vacuo* over P_2O_5 at 78°.

Anal. Calc'd for $C_{23}H_{27}N_7O_{10}$: C, 49.18; H, 4.84; N, 17.46. Found: C, 49.0; H, 4.98; N, 17.36.

L-Arginyl- β -phenyl-L-serine (acetate). α -*p*-Nitrocarbonyloxy- ω -nitro-*L*-arginyl- β -phenyl-*L*-serine (0.400 g.) was suspended in 95% ethanol (20 ml.) containing 25% of glacial acetic acid. The compound was hydrogenated for 18 hours at room temperature and at atmospheric pressure over 10% palladium on carbon (100 mg.). The catalyst was separated by filtration and the solvent was concentrated *in vacuo* at 30–40° to a volume of 10 ml.; the product then was precipitated with ether. The dipeptide was recrystallized from water-ethanol-ether. Yield: 0.298 g. (91%), m.p. 168–170° $[\alpha]_D^{22} +39.7^\circ$ (c, 0.73 in water). For analysis the product was dried for 18 hours *in vacuo* at 78°.

Anal. Calc'd for $C_{17}H_{27}N_5O_6$: C, 51.4; H, 6.8; N, 17.6. Found: C, 51.1; H, 6.7; N, 17.6.

The products and intermediates prepared are shown in Tables I and II.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF MONTREAL
MONTREAL, CANADA

The Conjugative Ability of Substituent Groups

LEON D. FREEDMAN AND G. O. DOAK

Received March 12, 1956

The effect of substituents on the reactivity of the benzene ring and of side chains attached to it can be quantitatively described by means of the Hammett equation:¹

$$\log k - \log k^\circ = \rho\sigma$$

The ρ and σ constants are being used by an ever-increasing number of investigators not only for summarizing experimental data but also for making various deductions about the nature of substituents. The present note is concerned with the use of substituent constants for determining the conjugative ability of electron-attracting groups.

Hammett found that in one case, that of the *p*-nitro group, it is impossible to use a single value of σ for all reactions; two distinctly different values are necessary. The larger of these (called σ^* by Jaffé²) gives satisfactory results with reactions of aniline and phenol derivatives; the other value (the "normal" σ value) applies to reactions to all other compounds. Table I lists the electron-attracting groups which are now known to require two substituent constants.

This duality of substituent constants has been interpreted as evidence for resonance interaction of the substituent with amino, hydroxy, and similar

groups.³ Furthermore, some authors⁴ have assumed that the magnitude of the difference between σ^* and σ may be taken as a measure of the conjugative ability of a substituent. If this assumption is correct, the substituents in Table I should be in order of their conjugative ability. For the most part, the relative order of the conjugative ability does not appear unreasonable. There is, however, a striking anomaly. The difference between σ^* and σ for the *p*-carboxy group places it near the top of the list; the corresponding difference for the *p*-carboethoxy group is near the bottom. It does not seem likely that two such similar groups have such different conjugative abilities.

TABLE I
GROUPS WITH TWO SUBSTITUENT CONSTANTS

Group	$\sigma^* - \sigma$
<i>p</i> -CHO	0.91 ^a
<i>p</i> -NO ₂	.49 ^b
<i>p</i> -COOH	.46 ^a
<i>p</i> -CN	.37 ^a
<i>p</i> -COCH ₃	.36 ^a
<i>p</i> -SO ₂ CH ₃	.32 ^c
<i>p</i> -S(CH ₃) ₂ ⁺	.26 ^d
<i>p</i> -SOCH ₃	.25 ^e
<i>p</i> -SO ₃ ⁻	.21 ^f
<i>p</i> -Si(C ₆ H ₅) ₃	.20 ^g
<i>p</i> -PO(OC ₂ H ₅) ₂	.19 ^h
<i>p</i> -Ge(C ₆ H ₅) ₃	.16 ^g
<i>p</i> -COOC ₂ H ₅	.16 ^c
<i>p</i> -Si(CH ₃) ₃	.14 ⁱ

^a The value for σ^* was taken from ref. 1; the value for σ was taken from ref. 2. ^b Taken from ref. 1. ^c Taken from ref. 2. ^d Taken from ref. 4b. ^e Taken from Bordwell and Boutan, *Abstracts of Papers, 124th Meeting, American Chemical Society, Chicago, Ill., September, 1953*, p. 81-O. ^f Taken from Zollinger, *Nature*, **172**, 257 (1953). ^g Taken from ref. 4c. ^h Taken from Freedman and Jaffé, *J. Am. Chem. Soc.*, **77**, 920 (1955). ⁱ Taken from ref. 4a.

According to Sklar,⁵ the effect of a substituent on the ultraviolet absorption spectrum of benzene depends mainly on the degree of resonance interaction between the substituent and the phenyl radical. Since we have found (*cf.* Table II) that the spectra of benzoic acid and ethyl benzoate are virtually identical, there is probably no appreciable difference between the conjugative effects of the *p*-carboxy and the *p*-carboethoxy groups. Doub and Vandenbelt⁶ have concluded that the displacement of the "primary absorption band" of benzene may

(3) (a) Branch and Calvin, *The Theory of Organic Chemistry*, Prentice-Hall, Inc., New York, N. Y., 1941, pp. 257, 417; (b) Bordwell and Cooper, *J. Am. Chem. Soc.*, **74**, 1058 (1952); (c) Bordwell and Anderson, *J. Am. Chem. Soc.*, **75**, 6019 (1953).

(4) (a) Benkeser and Krysiak, *J. Am. Chem. Soc.*, **75**, 2421 (1953); (b) Bordwell and Boutan, *J. Am. Chem. Soc.*, **78**, 87 (1956); (c) Benkeser, DeBoer, Robinson, and Sauve, *J. Am. Chem. Soc.*, **78**, 682 (1956).

(5) Sklar, *J. Chem. Phys.*, **7**, 984 (1939).

(6) Doub and Vandenbelt, *J. Am. Chem. Soc.*, **69**, 2714 (1947).

(1) Hammett, *Physical Organic Chemistry*, McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter VII.

(2) Jaffé, *Chem. Revs.*, **53**, 191 (1953).

be used as a measure of the resonance effect of a substituent. If this conclusion is valid, the order of groups in Table II should parallel their conjugative ability. It is immediately obvious that the order of groups in Table II is quite different from the order in Table I. In particular, the carboethoxy group is higher than five other groups in Table II, but lower than the same five groups in Table I. It is also seen that the spectrum of tetraphenylsilane indicates that little or no resonance exists between the silicon atom and the benzene ring. An investigation^{4c} of substituent constants, on the other hand, led to the opposite conclusion.

TABLE II
THE EFFECT OF SUBSTITUENTS ON THE PRIMARY (203.5 $m\mu$)
BAND OF BENZENE

C_6H_5X X =	$\lambda_{max} - 203.5$ $m\mu$
NO_2	65.0 ^a
CHO	46.0 ^a
$COCH_3$	42.0 ^a
$COOC_2H_5$	27.0 ^b
COOH	26.5, ^a 26.5 ^c
CN	20.5 ^a
$S(CH_3)_2^+$	16.5 ^d
SO_2CH_3	13.5 ^e
$Si(C_6H_5)_3$	0 ^f

^a Taken from ref. 6. ^b The ultraviolet absorption spectrum of ethyl benzoate was determined in 2% methanol according to the procedure previously described by Jaffé and Freedman, *J. Am. Chem. Soc.*, **74**, 1069 (1952); maxima at 230.5 $m\mu$ and 273 $m\mu$ (ϵ 11,100 and 890 respectively). ^c The spectrum of benzoic acid was determined in 0.1 *N* hydrochloric acid; maxima at 230 $m\mu$ and 273 $m\mu$ (ϵ 11,600 and 990 respectively). ^d Taken from ref. 4b; water was used as the solvent. ^e Taken from Fehnel and Carmack, *J. Am. Chem. Soc.*, **71**, 231 (1949); absolute ethanol was used as the solvent.

^f The spectrum of tetraphenylsilane was determined in 95% ethanol; maxima at 203.5 $m\mu$, 254 $m\mu$, 260 $m\mu$, and 264.5 $m\mu$ (ϵ 48,000, 1480, 1590, and 1450 respectively). The spectrum of this compound was previously determined by Milazzo, *Gazz. chim. ital.*, **71**, 73 (1941); *Chem. Abstr.*, **37**, 1928 (1943).

It should be emphasized, we believe, that the values of substituent constants are subject to appreciable errors.⁷ Since the differences between σ^* and σ are, of course, liable to even larger errors, it seems unwise to rely on the magnitude of these differences as a measure of the conjugative ability of substituent groups.

VENEREAL DISEASE EXPERIMENTAL LABORATORY
U. S. PUBLIC HEALTH SERVICE
SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF NORTH CAROLINA
CHAPEL HILL, NORTH CAROLINA

(7) Cf. Table 8 of ref. 2.

Reactions of Organometallic Compounds with Pyridazine¹

ROBERT L. LETSINGER AND RALPH LASCO

Received March 12, 1956

We have observed that pyridazine can be alkylated (or arylated) by means of organometallic compounds, and that such reactions may be used for the preparation of either 3- or 4-substituted pyridazines. Data on four typical reactions are summarized in Table I.

TABLE I
REACTIONS OF ORGANOMETALLIC COMPOUNDS WITH
PYRIDAZINE

Reaction	Organo-metallic Compound	Solvent	Position of Substitution in Isolated Product	Percentage Yield of Substituted Pyridazine
1	C_6H_5MgBr	Ether	4	7.3
2	C_6H_5Li	Ether	3	17
3	C_4H_9MgBr	Ether-tetrahydrofuran	4	23
4	C_4H_9Li	Ether	3	51

4-Substituted pyridazines were isolated from the Grignard reactions, and 3-substituted derivatives from the lithium reactions. The solvent is also a factor in the orientation, for a mixture of 3- and 4-butylpyridazine was obtained from a reaction of butyllithium with pyridazine in a mixed ether-tetrahydrofuran solvent.

The phenylpyridazines were characterized by their melting points and by derivatives; and the butylpyridazines, which were liquids, by oxidation to the known 3- and 4-pyridazinecarboxylic acids. Since the yields of the acids from these oxidations were of the order of 32–41%,² the possibility cannot be excluded that the products from reactions 3 and 4 were contaminated by some of the isomeric compound. The substance labeled 4-butylpyridazine seems to be essentially pure, however, for it was converted in 93% yield to a *picrate*, which melted at 107.5–108.5°. 3-Butylpyridazine did not form a crystalline *picrate*. Substituted pyridazines were

(1) Financial support for this work came from the Research Corporation.

(2) Variable yields have been reported for the pyridazinecarboxylic acids produced from oxidation reactions. Thus, (a) Poppenberg, *Ber.*, **34**, 3267 (1901), was unable to isolate any carboxylic acid from an oxidation of 3-methylpyridazine. On the other hand, (b) Leanza, Becker, and Rogers, *J. Am. Chem. Soc.*, **75**, 4086 (1953), obtained an 81% yield of 3-pyridazinecarboxylic acid from 3-hydroxymethylpyridazine, and (c) Gabriel and Colman, *Ber.*, **32**, 407 (1899), a 28% yield of the same acid from 3-*p*-hydroxyphenylpyridazine.