

DETERMINATION OF σ_p CONSTANTS OF 2-FURYL SUBSTITUENTS.
TRANSFER OF THE SUBSTITUENT EFFECT
THROUGH THE FURAN-BENZENE SYSTEM*

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para-Substituted (2-X-5-furyl)benzoic acids (X = H, CH₃, C₂H₅, CHO, COCH₃, Br, I, CN, CH₂OH, NO₂) were prepared. The apparent pK_a values of these derivatives were determined in the water-ethanol mixture at 25°C and used in calculations of the σ_p constants of the 2-X-5-furyl type substituents by means of the Hammett equation. The thus-obtained data are discussed with respect to the transfer of the substituent effect through the furan-benzene system.

Quantitative aspects of electron effects in the 2-furyl substituent have been investigated by Fringuelli and coworkers¹. On the basis of σ , σ^+ , and σ^- values for the furan nucleus, a strong conjugation effect of the 2-furyl substituent in both directions has been observed. The aim of the present work is to determine the character of the substituted furan nucleus attached to the *para*-position of benzoic acid as substituent. Substituted 2-X-5-(4-carboxyphenyl)furan derivatives A (X = H, CH₃, C₂H₅, CHO, Br, CH₃CO, CN, NO₂, I, CH₂OH) have been therefore prepared. The σ_p constants of the corresponding 2-X-5-furyl type substituents, designated as $\sigma_p(X-C_4H_2O)$, have been calculated by means of the Hammett equation^{2,3} from the apparent pK_a values of the above substituted benzoic acids.

The pK_a values of benzoic acids carrying a substituted furan nucleus were determined potentiometrically in the water-ethanol mixture (1 : 1, v/v) at $25 \pm 0.2^\circ\text{C}$. The impossibility to determine the thermodynamic dissociation constants is due to insolubility of the present derivatives in pure water. The $\sigma_p(X-C_4H_2O)$ substituent constants were calculated on the basis of the Hammett equation from the difference of pK_a values of benzoic acid and 2-X-5-(4-carboxyphenyl)furan. The equation was used because of the negligible direct mutual resonance interaction between the substituent and the reaction center. The pK_a value (5.71) of unsubstituted benzoic acid is in accordance with values reported in the literature (5.74; 5.70; 5.73; 5.80; ref.^{1,4,5,6} resp.); some differences in the pK_a value of benzoic acid are due to the use of glass

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electrode and the water-ethanol solvent system³. For the pK_a values and the calculated $\sigma_p(X-C_4H_2O)$ data see Table I.

TABLE I

The (Apparent) pK_a Values of *para*-Substituted (2-X-5-Furyl) Benzoic Acids and Calculated $\sigma_p(X-C_4H_2O)$ Constants

Compound	X	pK_a^a	$\sigma_p(X-C_4H_2O)$	$\sigma_p(X-C_6H_4)^c$
I	H	5.86	-0.1 ^b	-0.01
II	CH ₃	5.97	-0.17	-0.03
III	C ₂ H ₅	5.96	-0.16	-
IV	OHC	5.78	-0.05	-
V	Br	5.712	-0.001	0.14
VI	CH ₃ CO	5.58	0.08	-
VII	NC	5.56	0.1	-
VIII	O ₂ N	5.40	0.20	0.30
IX	I	5.75	-0.03	-
X	HOCH ₂	5.89	-0.12	-

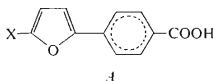
^a Ethanol-water (1 : 1, v/v) at 25°C; ^b reported¹, +0.02; ^c reported values⁹.

The strength of *para*-substituted (2-X-5-furyl)benzoic acids is a linear function of Hammett's σ_p constants of substituents attached to the furan nucleus. The slope of this dependence $pK_a - \sigma_p$ ($\rho = 0.555$, $r = 0.987$) is lower than ρ of substituted benzoic acids³ ($\rho = 1.522$) or substituted 2-furancarboxylic acids⁷ ($\rho = 2.12$). A similar linear dependence has been observed between the calculated $\sigma_p(X-C_4H_2O)$ constants and Hammett's σ_p constants ($r = 0.987$).

The calculated σ_p constant value of the 2-furyl substituent, $\sigma_p(X-C_4H_2O) = -0.1$, suggests a weak electron-donating character of the furan nucleus. This conclusion is in accordance with some earlier results⁸. A weak electron-donating character is also shown by those furan nuclei carrying as substituents 5-CHO ($\sigma_p = -0.05$), 5-Br ($\sigma_p = -0.001$), and 5-I ($\sigma_p = -0.03$). The occurrence of a weak electron-accepting character requires the presence of such strong deactivating substituents such as 5-COCH₃ ($\sigma_p = 0.08$) and 5-NO₂ ($\sigma_p = 0.20$). The calculated σ_p constant of the 2-furyl substituent indicates a shift of electrons from the furan nucleus into the benzene ring when the carboxylic group is attached to the benzene ring and the furan nucleus is unsubstituted.

Table I contains the $\sigma_p(X-C_6H_4)$ values as calculated by Berliner and Blomers⁹ from apparent pK_a data of substituted 4'-X-4-biphenylcarboxylic acids, along with

the corresponding calculated $\sigma_p(X-C_4H_2O)$ constants. It is obvious that benzene ring substituted by an electron-accepting substituent display a more pronounced electron-accepting character than an equally substituted furan ring. Furan ring substituted by an electron-donating substituent or the unsubstituted furan ring exhibits a more pronounced electron-donating character than an equally substituted benzene ring.



As indicated by the tangent value ($\rho = 0.555$) of the pK_a - σ linear dependence (Fig. 1), the transfer of the substituent effect through the furan-benzene system is more difficult than through the benzene nucleus alone ($\rho = 1.52$) or the furan nucleus alone ($\rho = 2.12$). The free energy linear dependence in the furan-benzene system requires the validity of the relation

$$\sigma_p(X-C_4H_2O) \cdot \rho_{Bz} = \sigma_p \cdot \rho_{FuBz},$$

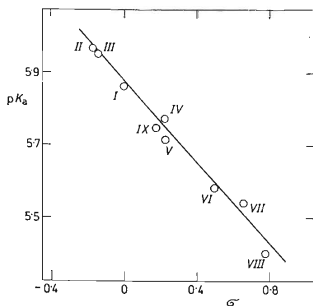


FIG. 1

Dependence of Apparent Dissociation Constants of 2-X-5-(4-Carboxyphenyl)furan Derivatives on σ_p Constants ($\rho = 0.555$, $r = 0.987$)

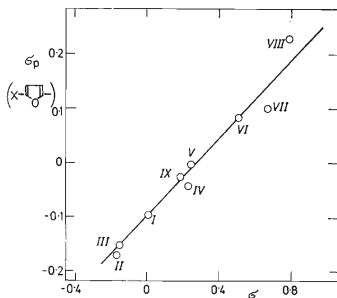


FIG. 2

Dependence of $\sigma_p(X-C_4H_2O)$ Constants on σ_p Constants of Substituents Attached to the Furan Nucleus ($\rho = 0.364$, $r = 0.987$) (for the numbering of derivatives see Table I)

wherein ρ_{Bz} is the tangent of the pK_a - σ dependence in the case of substituted benzoic acids and ρ_{FuBz} is the tangent of the pK_a - σ dependence in the case of 4-(5-X-2-furyl)-benzoic acids. The tangent of this linear dependence $\rho_{FuBz}/\rho_{Bz} = 0.364$ represents the transmission factor of the substituent effect transfer through the furan-benzene system in comparison with the substituent transfer through the benzene nucleus (Table II and Fig. 2). The lowered ability to transfer the substituent effect through the furan-benzene system when compared to benzene alone might be explained by a longer conjugated system as well as by the probable lack of coplanarity in the furan-benzene system.

TABLE II
Statistic Parameters of Correlations for Substituted 2-(4-Carboxyphenyl)furans

Correlation	n^a	r^b	ρ^c	s_{ρ}^d	q^e	s_q^f	s^g
pK_a - σ	9	0.987	0.555	0.032	5.87	0.024	0.031
$\sigma - \sigma_p(X-C_4H_2O)$	9	0.987	0.364	0.022	-0.105	0.016	0.021

^a Number of compounds used in the correlation; ^b correlation coefficient; ^c slope; ^d slope error; ^e calculated value for the unsubstituted compound; ^f error q ; ^g standard deviation.

EXPERIMENTAL

The apparent pK_a constants were determined by titration of the corresponding acids ($5 \cdot 10^{-3} M$ solutions) in ethanol-water (1 : 1, v/v) with 0.1M tetramethylammonium hydroxide in the nitrogen atmosphere at $25 \pm 0.2^\circ C$ and calculated from the Henderson equation¹⁰. Measurements were performed on the Research pH Meter Beckman GB using the Radiometer G 2222 C GU glass electrode, the Radiometer K 4112 calomel electrode, and the Radiometer ABU 1C automatic burette. Each pK_a value is an average of at least three measurements. Maximum deviation, ± 0.02 of the pH unit. The parameters of linear correlations were calculated on the Hewlett Packard 9810A Type computer. The IR spectra were taken on a UR-20 Zeiss spectrophotometer in tetrachloromethane (1 cm NaCl cell; concentration, about $2 \cdot 10^{-2} M$) in the $1600-1800 \text{ cm}^{-1}$ region.

2-(4-Carboxyphenyl)furan (I). A mixture of 4-aminobenzoic acid (0.1 mol), isopentyl nitrite (0.11 mol), and furan (500 ml) is maintained at $30^\circ C$ for 48 h, evaporated under diminished pressure, and the residue subjected to vacuum sublimation. Yield, 32.3% of compound I, m.p. $226^\circ C$ (ethanol); reported¹, m.p. $227^\circ C$ (ligroin-light petroleum). $\nu(\text{CO})$ 1690 cm^{-1} (dimer), 1736 cm^{-1} (monomer).

2-Alkyl-5-(4-carboxyphenyl)furans. A mixture of the corresponding carbonyl compound (0.01 mol), 80% aqueous hydrazine hydrate (0.03 mol), potassium hydroxide (0.05 mol), and diglycol (15 ml) is heated at $120^\circ C$ for 2 h. The water and excess hydrazine is distilled off, the residue cooled down, poured into water, and the mixture acidified. The following furans were prepared

by this procedure. 2-Methyl-5-(4-carboxyphenyl)furan (*II*), m.p. 226°C (ethanol). Yield, 99%. $\nu(\text{CO})$ 1687 and 1734 cm^{-1} . For $\text{C}_{12}\text{H}_{10}\text{O}_3$ (202.2) calculated: 71.20% C, 5.00% H; found: 71.11% C, 5.01% H. 2-Ethyl-5-(4-carboxyphenyl)furan (*III*), m.p. 177–179°C (ethanol). Yield, 93%. $\nu(\text{CO})$ 1688 and 1734 cm^{-1} . For $\text{C}_{13}\text{H}_{12}\text{O}_3$ (216.2) calculated: 72.20% C, 5.60% H; found: 72.25% C, 5.63% H.

5-(4-Carboxyphenyl)-2-furancarbaldehyde (*IV*). The preparation was performed according to ref.¹¹.

2-Bromo-5-(4-carboxyphenyl)furan (*V*). To a mixture of compound *I* (1.6 g; 0.085 mol), red phosphorus (0.1 g; 3.2 mmol), and chloroform (50 ml) there is added a solution of bromine (2.72 g; 1.7 mmol) in chloroform (30 ml) under agitation and reflux. When the reaction is finished (2 h), the mixture is cooled down, made alkaline with aqueous ammonia, filtered, and the filtrate acidified with dilute (10%) hydrochloric acid. Yield, 1.5 g (66%) of compound *V*, m.p. 256 to 258°C (ethanol); $\nu(\text{CO})$ 1692 and 1737 cm^{-1} . For $\text{C}_{11}\text{H}_7\text{BrO}_3$ (267.1) calculated: 49.45% C, 2.65% H, 29.80% Br; found: 49.48% C, 2.71% H, 29.70% Br.

5-(4-Carboxyphenyl)-2-acetylfuran (*VI*). The procedure of ref.¹¹ was used. Yield, 45% of compound *VI*, m.p. 240°C (ethyl acetate); $\nu(\text{CO})$ 1685, 1694, and 1738 cm^{-1} . For $\text{C}_{13}\text{H}_{10}\text{O}_4$ (230.2) calculated: 67.70% C, 4.38% H; found: 67.60% C, 4.38% H.

5-(4-Carboxyphenyl)-2-furonitrile (*VII*). The preparation was performed according to ref.¹².

2-Nitro-5-(4-carboxyphenyl)furan (*VIII*). A solution of compound *I* (0.01 mol) in acetic anhydride (20 ml) is added at -10°C to a mixture of 65% nitric acid (0.05 mol) and acetic anhydride (30 ml), and the whole is processed according to ref.¹³. Yield, 51% of compound *VIII*, m.p. 278°C (ethanol); $\nu(\text{CO})$ 1696 and 1741 cm^{-1} . For $\text{C}_{11}\text{H}_7\text{NO}_5$ (233.2) calculated: 56.60% C, 3.03% H, 6.10% N; found: 56.50% C, 3.00% H, 6.11% N.

2-Iodo-5-(4-carboxyphenyl)furan (*IX*). To an aqueous suspension (25 ml) of 0.046 mol of 2-chloromercuri-5-(4-carboxyphenyl)furan (prepared from 5.7 mmol of compound *I*, 5.8 mmol of mercuric chloride, 38.5 mmol of sodium acetate, and 100 ml of ethanol) there is added a solution of iodine (0.009 mol) and potassium iodide (0.018 mol) in water (15 ml) and the mixture is processed as usual to afford 54% of compound *IX*, m.p. 207–210°C (ethanol); $\nu(\text{CO})$ 1692 and 1736 cm^{-1} . For $\text{C}_{11}\text{H}_7\text{IO}_3$ (314.1) calculated: 42.00% C, 2.25% H; found: 42.13% C, 2.20% H.

2-Hydroxymethyl-5-(4-carboxyphenyl)furan (*X*). To a solution of compound *IV* (7.5 mmol) in ethanol (50 ml) there is added with stirring sodium borohydride (7.5 mmol) in ethanol (50 ml), the reaction allowed to proceed for 1 h, the mixture neutralised with 0.05M- H_2SO_4 , and processed as usual to afford 86% of compound *X*, m.p. 213–215°C (ethanol); $\nu(\text{CO})$ 1692 and 1737 cm^{-1} . For $\text{C}_{12}\text{H}_{10}\text{O}_4$ (218.2) calculated: 66.10% C, 4.63% H; found: 66.18% C, 4.62% H.

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