Transmission of Substituent Effects in Heterocycles. The Rates of Solvolysis of Substituted 1-(2-Thienyl)ethyl *p*-Nitrobenzoates[1]

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The rates of solvolysis of nine substituted 1-(2-thienyl)ethyl *p*-nitrobenzoates in 80% ethanol are well correlated by Brown's electrophilic substituent constants, $\sigma_m{}^+$ and $\sigma_p{}^+$ (correlation coefficient 0.993). An examination of the CNDO/2 molecular orbital parameters for 2-methylthiophene and 2-thienylmethyl cation reveal that this correlation is the result of the near coincidence of the regional charges at positions 4 and 5 in the thiophene moiety, with similar electron densities at the 3 and 4 positions of the benzene ring. The CNDO calculations carried out on thiophene appear to slightly underestimate the response of the system to changes in charge distribution. The slope of the correlation line (ρ) is -6.8 *vs.* $\sigma_p{}^+$, -7.1 against substituent constants determined by CNDO parameters, rather than -5.7 as observed for benzene systems.

Several studies have appeared recently which show that thiophene is more susceptible to electrophilic aromatic substitution than benzene. Marino and his coworkers have shown,[3] as have we,[4] that useful linear free energy relationships apply for electrophilic aromatic substitution reactions at the α and β positions of thiophene, and that the "Extended Selectivity" relationship holds.[3] Other recent studies[5,6] have shown that good correlation is observed for electrophilic reactions of a number of substituted thiophenes with Brown's σ^+ substituent constants.[7]

As there is a clear relationship between electrophilic substitution reactions and side chain solvolysis reactivity,[8-10] we have investigated solvolysis rates of substituted thiophene derivatives to gain information regarding the transmission of substituent effects in the thiophene ring system. In a previous study from these laboratories,[11] it was shown that this approach was useful in furan chemistry.

The solvolysis of 1-(2-thienyl)ethyl *p*-nitrobenzoate has a convenient rate near room temperature in 80% ethanol. The results of kinetic measurements on nine substituted derivatives are given in Table I. When these data are plotted against Brown's σ^+ constants, using $\sigma_p{}^+$ for 5 substituents and $\sigma_m{}^+$ for 4 substituents, an excellent correlation is obtained; ρ is -6.79 and the correlation coefficient is 0.993.

TABLE I

RELATIVE RATES OF SOLVOLYSIS OF SUBSTITUTED 1-(2-THIENYL)ETHYL *p*-NITROBENZOATES AT 25°

Compd	Rel rate	σ^{+a}	$\sigma_{ij}{}^{+d}$
5-OCH$_3$	1.61×10^5	-0.778	-0.728
5-Cyclopropyl	503	-0.410^b	-0.399
5-Methyl	81	-0.311	-0.305
5-Phenyl	15.4	-0.179	-0.152
H	1.00	0.00	0.00
5-Bromo	0.137	0.150	0.207
4-Bromo	0.00187	0.405	0.416
4,5-Dibromo	0.000693	0.555^c	0.623^e
4-Ethoxycarbonyl	0.000705	0.366	0.382
5-Ethoxycarbonyl	0.000121	0.482	0.575

[a] From ref 7 unless otherwise noted; $\sigma_p{}^+$ used for 5 substituents, $\sigma_m{}^+$ for 4 substituents. [b] From L. B. Jones and V. K. Jones, *Tetrahedron Lett.*, 1493 (1966). [c] Sum of $\sigma_m{}^+$ and $\sigma_p{}^+$. [d] From eq 2, *vide infra.* [e] Sum of $\sigma_{5-2}{}^+$ and $\sigma_{4-2}{}^+$.

We have carried out a further investigation of these results to examine the potentialities of molecular orbital calculations to deal with these results. Recently, Butler[12] has reported that the observed values for the dissociation constants of substituted thienoic acids are well reproduced by the Dewar–Grisdale method,[13] using the SCF-π parameters of Summerfield and Kreevoy.[14] It should be further noted that there is high-quality correlation with the original Hammett substituent constants, as noted by Jaffé and Jones,[15] and more recently by Freeman[16] for the dissociation constants of the substituted thienoic acids. The calculated σ constants (Dewar–Grisdale) of Butler are very similar in value to the original Hammett σ values.

Bancroft and Howe[17] have shown that the Dewar–Grisdale equation,[13] when calibrated with Brown's σ^+ constants[7] rather than Hammett σ constants, gives greatly improved results in correlating the measured rates of detritiation of substituted naphthalenes. Eaborn and Fischer[18] have extended these observations.

Application of a modification of the Dewar–Grisdale equation successfully treats the substituent effects in the solvolysis of a variety of heteroarylmethyl compounds. The Dewar–Grisdale equation (1) possesses

$$(\sigma_{ij})_x = F_x/r_{ij} + q_{ij}M_x \qquad (1)$$

a term $(g_{ij}M_x)$ representative of resonance effects. M_x is a parameter indicative of the resonance capability of substituent and g_{ij} is a measure of the transmission of resonance effects from a substituent attached to ring carbon i to the carbon (j) bearing the reaction center. The term g_{ij} is derived from Hückel molecular orbital

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[2] NIH Predoctoral Fellow, 1968–1970 (GM 41,892).

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theory. In solvolysis the delocalization of charge from the side chain to the carbon bearing the substituent, rather than polarization of the ring by the substituent, is of prime importance. Furthermore, the appreciable polarization of neutral heterocyclic systems necessitates consideration of the charge distribution of the unionized initial state as well. Accordingly, we define the term Δq_{ij} as the difference in regional charge[19] at atom i in the un-ionized molecule and the heteroarylmethyl cation. Use of the Δq_{ij} term in the framework of 1 gives the modified Dewar–Grisdale equation (2), in

$$(\sigma_{ij}^+)_x = F_x^+/r_{ij} + \Delta q_{ij} M_x^+ \qquad (2)$$

which F^+ is a measure of the field set up by the substituent, M^+ is a measure of the capacity for resonance interaction of the substituent, and r_{ij} is the distance between atoms i and j. F^+ and M^+ constants are established for each substituent by the use of Brown's σ_p^+ and σ_m^+ constants in conjunction with $1/r_{ij}$ and Δq_{ij} values appropriate to the toluene–benzyl cation pair. Effective substituent constants, σ_{ij}^+, can then be calculated for any aromatic system from eq 2.

In practice the Δq_{ij} terms are obtained from molecular orbital calculations. The charge distributions of neutral compounds are computed with use of a methyl group as a side chain model; replacement of the methyl group with a planar methylene provides the computational model for the carbonium ion. The availability of standard programs for CNDO/2 and INDO all-valence electron molecular orbital models[20] made it feasible to compute Δq_{ij} values for a wide variety of heterocyclic systems. Such methods, by virtue of their uniquely defined heteroatom parameters and overall superiority to Hückel molecular orbital theory, are well suited to this application.

Two particular features of this approach are to be noted. The F^+_{INDO} and M^+_{INDO} values for typical substituents[21] show nearly complete separation into field ($\mathcal{F}$) and resonance ($\mathcal{R}$) terms when analyzed in terms of the Swain and Lupton model[22] ($F^+_{\mathrm{INDO}} = 91\%\ \mathcal{F}$, $M^+_{\mathrm{INDO}} = 95\%\ \mathcal{R}$). In addition, this approach is particularly suitable for predictions for new systems.

In the present instance, these methods show very clearly the reasons for the high quality of the correlation reported above with σ_p^+ and σ_m^+. This is the result of the near coincidence in the regional charges[20] at positions 4 and 5 in the thiophene ring, and the corresponding positions, meta or para, respectively, in benzene. Hence, the solvolysis reaction rate should respond to that blend of field and resonance interaction which is closely represented by σ_p^+ and σ_m^+.

The quality of the correlation using σ_{ij}^+ values from molecular orbital parameters is very similar to that using simply σ_p^+ and σ_m^+. Thus for the thiophene series the F^+, M^+, CNDO/2 method offers little advantage over the simple σ_p^+, σ_m^+ correlation. For furans, however, F^+, M^+, and CNDO/2 or INDO methods provide a clear improvement.[23]

The value of the correlation slope ρ for the CNDO/2 calculations is −7.14, somewhat more negative than the value (−5.7) typical of the solvolysis rates for secondary benzylic esters. In the case of furan[23] we observed that ρ was the same as for the benzene series within the experimental uncertainty; for benzofurans,[23] ρ is likewise the same for the benzyl compounds. It would thus appear that the CNDO calculations appropriately reproduce the balance of charge density at position 4 *vis-a-vis* position 5 in thiophene; however, it appears that the method slightly underestimates the magnitude of the charge induced on changing from the neutral methyl arene to the thienylmethyl cation.

Table II gives the results of the CNDO/2 calculations. The change in regional charge, Δq,[19] which results from the conversion of the methyl heteroarene to the heteroarylmethyl cation (A → B) is tabulated for benzene (toluene → benzyl) and for thiophene (2-methylthiophene → 2-thienylmethyl). The close similarity of the change in charge density is to be noted.

TABLE II

RESULTS OF CNDO/2 CALCULATIONS FOR BENZENE AND THIOPHENE

System	Position i	Position j	r	Δq	% $\mathcal{R}$
Benzene	3	1	1.732	0.0368	33
Benzene	4	1	2.000	0.2115	65
Thiophene	4	2	1.672	0.0395	~35
Thiophene	5	2	1.768	0.2051	65
Furan	4	2	1.605	0.0642	40

For typical substituents, one may calculate the ratio of the field and resonance components, using the Swain and Lupton approach.[22]

The percentage resonance predicted in the thiophene series (column 5, Table II) is nearly identical with the percentage resonance derived by Swain and Lupton from the σ^+ constants of Brown and Okamoto.

The differentiation between thiophene and furan derivatives is finally indicated by one entry for furan in Table II. The 4-substituted 2-furyl system is expected to show a greater resonance component, an expectation in accord with our observations.[23]

Experimental Section[24]

5-Bromo-2-acetylthiophene was prepared from 2-bromothiophene by the method of Hartough and Conley[25] in 88% yield, mp 87–89° (lit.[25] mp 94–95°).

5-Methyl-2-acetylthiophene was prepared from 2-methylthiophene by the method of Hartough and Kosak[26] in 71% yield, bp 90–92° (4 mm) [lit.[26] bp 84.5° (2 mm)].

5-Phenyl-2-acetylthiophene was prepared from 2-phenylthiophene[27] by the method of Hartough and Kosak[26] in 52% yield, mp 113–114° (lit.[28] mp 115–116°).

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(19) Regional charge: The sum of the charges on a carbon atom and on any hydrogen atoms bonded to it. A. Streitwieser, Jr., and R. G. Jesaitis in "Sigma Molecular Orbital Theory," O. Sinanoglu and K. B. Wiberg, Ed., Yale University Press, New Haven, Conn., 1970, p 197.

(20) Programs available from the Quantum Chemistry Program Exchange, University of Indiana. We wish to express our appreciation to Professor Streitwieser and Dr. P. Mowery for providing us with the programs and in counsel in their use.

(21) A set including $-OMe$, $-CH_3$, $-C_2H_5$, $-Cl$, $-Br$, $-H$, $-CO_2Et$, $-CN$, $-CF_3$, and NO_2.

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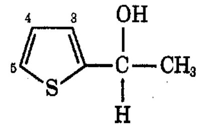
TABLE III

NMR CHEMICAL SHIFTS[a] AND COUPLING CONSTANTS[b] OF SUBSTITUTED 1-(2-THIENYL)ETHANOLS



Registry no.	Compd	Solvent	δ H_3	δ H_4	δ H_5	δ CH_3	δ CH	δ OH[c]	Additional data
2309-47-9	Unsubstituted	CCl_4	6.8 (m)	6.8 (m)	7.03 (m)	1.42 (d)	4.84 (q)	4.03 (s)	$J_{CH_3-CH} = 7$
34878-39-2	5-Cyclopropyl	CCl_4	6.58 (d)	6.46 (d)		1.44 (d)	4.82 (s)	3.32 (s)	$J_{CH_3-CH} = 7$; $J_{3,4} = 3.5$; $CH_{(cyclopropyl)}$, δ 1.9 (m); $CH_{2(cyclopropyl)}$, δ 0.7 (m)
34878-40-5	5-Methyl	$CDCl_3$	6.62 (d)	6.48 (d)		1.41 (d)	4.83 (q)	4.15 (s)	$J_{CH_3-CH} = 7$; 5-CH_3, δ 2.33 (s); $J_{3,4} = 3.3$
34878-41-6	5-Bromo	Neat	6.50 (d)	6.84 (d)		1.38 (d)	4.82 (q)	4.90 (s)	$J_{CH_3-CH} = 7$; $J_{3,4} = 3.5$
1665-38-9	5-Phenyl	$CDCl_3$	6.83 (d)	7.06 (d)		1.57 (d)	5.00 (q)	3.12 (s)	$J_{CH_3-CH} = 7$; $J_{3,4} = 3.5$; 5-phenyl, δ 7.3 (m)
34878-43-8	5-Ethoxycarbonyl	CCl_4	6.80 (d)	7.49 (d)		1.48 (d)	4.98 (q)	4.27 (s)	$J_{CH_3-CH} = 7$; $J_{3,4} = 3$; $CH_{3(Et)}$, δ 1.33 (t); $CH_{2(Et)}$, δ 4.20 (q); $J_{CH_3-CH_2} = 7$
34878-44-9	4,5-Dibromo	CS_2	6.60 (s)			1.42 (d)	4.78 (q)	4.28 (s)	$J_{CH_3-CH} = 7$
34878-45-0	4-Ethoxycarbonyl	CCl_4	7.09 (d)		7.73 (d)	1.48 (d)	4.85 (q)	4.16 (s)	$J_{CH_3-CH} = 7$; $J_{3,5} = 1.2$ $CH_{3(Et)}$, δ 1.3 (d); $CH_{2(Et)}$, δ 4.18 (q); $J_{CH_3-CH_2} = 7$
34878-46-1	4-Bromo	Neat	6.75 (d)		7.00 (d)	1.36 (d)	4.83 (q)	4.85 (s)	$J_{CH_3-CH} = 7$; $J_{3,5} = 2$

[a] In parts per million (δ) from internal TMS. [b] *J*, the observed coupling constant, in cps. [c] Multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

4-Bromo-2-acetylthiophene and 4,5-dibromo-2-acetylthiophene were prepared from 2-acetylthiophene by the method of Gol'dfarb and Vol'kenshtein.[29] 4-Bromo-2-acetylthiophene was obtained in 51% yield, bp 132–134° (15 mm) [lit.[29] bp 133° (15 mm)]. The yield of 4,5-dibromo-2-acetylthiophene was 37% of white needles (ethanol), mp 83.5–84.5° (lit.[29] mp 85–86°).

4-Ethoxycarbonyl-2-acetylthiophene was prepared by a modification of the method of Farrar and Levine.[30] To 24.0 g (0.153 mol) of 3-ethoxycarbonylthiophene[31] in a three-neck 250-ml flask equipped with a reflux condenser and an overhead stirrer was added 18.15 g (0.178 mol) of acetic anhydride. To the stirred solution was added 4 ml of a 47% solution of boron trifluoride etherate by means of a hypodermic syringe. The flask was sealed and heated on a steam bath for 3 hr. The resulting black oil was poured into 1 l. of water and extracted with 3 × 50 ml of ether. The ether solution was washed with 2 × 50 ml of saturated sodium bicarbonate solution and once with 50 ml of water. After drying over anhydrous magnesium sulfate, the ether was stripped off on a rotary evaporator. Distillation at 5 mm gave 9.7 g of recovered starting material, bp 79–80°, and a fraction of a colorless oil, bp 140–144°, which soon solidified. Crystallization from hexane gave 6.8 g of colorless needles, mp 79.5–80.5°, of 4-ethoxycarbonyl-2-acetylthiophene. Imoto and coworkers[32] report the boiling point as 150–152° (6 mm).

2-Methyl-2-[2-(5-carboxythienyl)]-1,3-dioxolane was prepared by a modification of the method of Thames and McCleskey.[33] To 17.2 g (0.101 mol) of 2-methyl-2-(2-thienyl)-1,3-dioxolane dissolved in 150 ml of anhydrous ether under a nitrogen atmosphere was added 62.6 ml (0.101 mol) of *n*-butyllithium in hexane at room temperature. The solution gradually turned brown upon stirring for 1 hr. After cooling in an ice-salt bath for 10 min the brown solution was poured over freshly ground Dry Ice. The reaction mixture was allowed to warm until all the Dry Ice had evaporated. The organic layer was extracted with 200 ml of dilute sodium hydroxide solution. The aqueous solution was washed with 3 × 100 ml of ether which was backwashed with 50 ml of dilute sodium hydroxide solution. The aqueous portions were combined and cautiously acidified with concentrated hydrochloric acid to a pH of 3. Cooling of this acidic solution resulted in formation of a flocculent yellow solid. The solid was collected by suction filtration. The aqueous filtrate was extracted with 2 × 50 ml of ether. The ether solution was dried over anhydrous calcium chloride and the solvent was removed on the rotary evaporator. The resulting yellow solid was combined with that previously obtained to give 11.1 g of crude 2-methyl-2-[2-(5-carboxythienyl)]-1,3-dioxolane. The structure of the product was established by examination of the nmr spectrum. Less than 5% of an acetyl methyl peak resulting from hydrolysis of the dioxolane ring could be observed. The mixture of products was not separated but the crude material was directly used for the preparation of 5-ethoxycarbonyl-2-acetylthiophene.

5-Ethoxycarbonyl-2-acetylthiophene.—To a solution of 400 ml of absolute ethanol and 10 ml of concentrated sulfuric acid was added 10.8 g (0.05 mol) of crude 2-methyl-2-[5-carboxythienyl)]-1,3-dioxolane. The mixture was heated under reflux on a steam bath for 2.5 hr. The warm solution was poured into 1200 ml of sodium carbonate solution in a 3-l. separatory funnel. The flocculent yellow solid was taken up into 250 ml of ether. The aqueous ethanol phase was extracted with 4 × 50 ml of ether. The ether extracts were combined and dried over anhydrous calcium chloride. The solvent was removed under reduced pressure to give a yellow solid. Two recrystallizations gave 5.8 g (56%) of beige-colored 2-acetyl-5-ethoxycarbonylthiophene, mp 54–54.5°.

1(2-Thienyl)ethanols were prepared by reducing the ketones with sodium borohydride in anhydrous methanol for 1 hr at room temperature. Work-up in the usual fashion and removal of the solvent on a rotary evaporator generally yielded 90% of the carbinol. The 4- and 5-ethoxycarbonyl compounds were reduced in anhydrous ethanol instead of methanol to avoid transesterification. All the alcohols were characterized by nmr. The data are recorded in Table III.

1-(5-Methoxy-2-thienyl)ethanol was prepared from 2-methoxythiophene.[34] To 10.0 g (0.0885 mol) of 2-methoxythiophene in 250 ml of dry ether (dried over sodium) at 0° was added 57.5 ml

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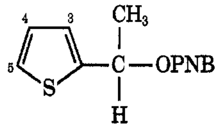
TABLE IV

NMR CHEMICAL SHIFTS[a] AND COUPLING CONSTANTS[b] OF SUBSTITUTED 1-(2-THIENYL)ETHYL *p*-NITROBENZOATES



Registry no.	Compd	Solvent	δ H_3	δ H_4	δ H_5	δ CH_3	δ CH	δ C_6H_4	Additional data
23516-71-4	Unsubstituted	$CDCl_3$	7.1 (m)[c]	7.1 (m)	7.32 (q)	1.82 (d)	6.46 (q)	8.24 (s)	$J_{CH_3-CH} = 7$; $J_{4,5} = 5$; $J_{3,5} = 1.5$
34878-48-3	5-Methoxy	CS_2	6.62 (d)	5.89 (d)		1.76 (d)	6.12 (q)	8.07 (s)	$J_{CH_3-CH} = 7$; $J_{3,4} = 4$; $CH_{3(OCH_3)}$, δ 3.77 (s)
34878-49-4	5-Cyclopropyl	CCl_4	6.79 (d)	6.50 (d)		1.74 (d)	6.24 (q)	8.10 (s)	$J_{CH_3-CH} = 7$; $J_{3,4} = 4$; $CH_{(cyclopropyl)}$, δ 1.8 (m); $CH_{2(cyclopropyl)}$, δ 0.8 (m)
34878-50-7	5-Methyl	CS_2	6.82 (d)	6.53 (m)		1.70 (d)	6.25 (q)	8.12 (s)	$J_{CH_3-CH} = 7$; $J_{3,4} = 4$; 5-CH_3, δ 2.40 (d); $J_{(5-CH_3-CH)} = 0.4$
34878-51-8	5-Bromo	CS_2	6.80 (s)	6.80 (s)		1.73 (d)	6.20 (q)	8.10 (s)	$J_{CH_3-CH} = 7$
34878-52-9	5-Phenyl	CS_2	7.01 (s)	7.01 (s)		1.76 (d)	6.30 (q)	8.10 (s)	$J_{CH_3-CH} = 7$; 5-phenyl, δ 7.3 (m)
34878-53-0	5-Ethoxycarbonyl	$CDCl_3$	7.09 (d)[c]	7.64 (d)		1.81 (d)	6.38 (q)	8.23 (s)	$J_{CH_3-CH} = 7$; $J_{3,4} = 3.5$; $CH_{3(Et)}$, δ 1.35 (t); $CH_{2(Et)}$, δ 4.32 (q); $J_{CH_3-CH_2} = 7$
34878-54-1	4-Bromo	$CDCl_3$	7.06 (d)		7.18 (d)	1.78 (d)	6.36 (q)	8.23 (s)	$J_{CH_3-CH} = 7$; $J_{3,5} = 1.5$
34878-55-2	4,5-Dibromo	$CDCl_3$	6.92 (s)			1.77 (d)	6.28 (q)	8.20 (s)	$J_{CH_3-CH} = 7$
34878-56-3	4-Ethoxycarbonyl	$CDCl_3$	7.46 (d)		7.92 (d)	1.79 (d)	6.29 (q)	8.08 (s)	$J_{CH_3-CH} = 7$; $J_{3,5} = 1.5$; $CH_{3(Et)}$, δ 1.34 (t); $CH_{2(Et)}$, δ 4.26 (q); δ 4.26 (q); $J_{CH_3-CH_2} = 7$

[a] In parts per million (δ) from internal TMS. [b] *J*, the observed coupling constant, in cps. [c] Multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

(0.0885 mol) of *n*-butyllithium (Foote Mineral) in hexane in a slow stream. The stirred solution was maintained under nitrogen for 10 min. To the solution was added dropwise 5.85 g (0.0885 mol) of acetaldehyde which had been precooled in the refrigerator. The solution was stirred at 0° for 40 min. The reaction mixture was then refluxed under a nitrogen atmosphere using a Dry Ice–isopropyl alcohol condenser for 3 hr. The red liquid was poured over crushed ice and the ether layer was extracted and dried over anhydrous sodium sulfate. Removal of the ether at room temperature gave an amber oil whose nmr spectrum showed it to be 89% of the desired alcohol and 11% 2-methoxythiophene. Stringent efforts to maintain anhydrous conditions during the reaction or changing the temperature to −70° did not affect the product ratio. The production of 2-methoxythiophene is the result of a competing reaction in which the 5-methoxy-2-thienyllithium abstracts an acidic hydrogen from the acetaldehyde.

The crude alcohol was warmed to 35° and all of the 2-methoxythiophene was removed at a pressure of 0.1 mm over a period of 48 hr. The alcohol proved to be thermally unstable under normal distillation conditions. It could be purified, however, by a bulb-to-bulb transfer in a sealed system which had been evacuated to 0.01 mm prior to heating. The crude alcohol was kept in one bulb over anhydrous sodium carbonate and was gently warmed between 60 and 80°. The receiving bulb was cooled in a liquid nitrogen bath. In this manner 9.0 g (65%) of pale yellow 1-(5-methoxy-2-thienyl)ethanol was obtained. The alcohol was immediately used for the preparation of the *p*-nitrobenzoate ester.

1-(5-Cyclopropyl-2-thienyl)ethanol was prepared from 2-cyclopropylthiophene.[35] To a solution of 4.103 g (0.033 mol) of 2-cyclopropylthiophene dissolved in 100 ml of anhydrous ether under a nitrogen atmosphere was added 20.46 ml (0.033 mol) of *n*-butyllithium in hexane. The *n*-butyllithium solution was added to the stirred solution at 0° in a steady stream. During the course of addition the solution turned a pale brown color. The ice bath was removed after 10 min, and the solution was stirred at room temperature for 5 hr. To the stirred solution was added 3.4 ml (0.06 mol) of acetaldehyde, which had been precooled to 0°, by means of a dry syringe which had also been cooled. The mixture was allowed to stir for 20 min and then was washed with 100 ml of water. The wash water was back extracted with 2 × 50 ml of ether. The combined organic extracts were finally washed with 50 ml of water. The solution was dried over anhydrous magnesium sulfate and the solvent was removed at room temperature under reduced pressure to give 5.2 g of a reddish oil. Examination of this oil by nmr showed it to be about 70% of the desired alcohol. Chromatography on silica gel gave 0.9 g of 2-cyclopropylthiophene, eluted with petroleum ether (bp 30–60°), and 3.3 g (59.5%) of 1-(5-cyclopropyl-2-thienyl)ethanol, eluted with chloroform.

Substituted 1-(2-Thienyl)ethyl *p*-Nitrobenzoates.—The appropriate 1-(2-thienyl)ethanol was dissolved in 20 ml of cold pyridine and treated with freshly recrystallized *p*-nitrobenzoyl chloride. After 6 hr at room temperature, the mixture was gently warmed with 100 ml of hexane for 10 min. The hexane–pyridine solution was decanted and filtered and then washed with 4 × 50 ml of warm water. The pyridine-free hexane solution was dried by filtering through a sodium chloride mat. Cooling of the hexane solution gave the crystalline *p*-nitrobenzoate ester. This work-up gave better results, as many *p*-nitrobenzoates have low melting points and readily form oils. The nmr data for the *p*-nitrobenzoates are recorded in Table IV. Table V tabulates melting points and analyses.

2-Vinylthiophene was prepared by the method of Emerson and Patrick[36] in 43% yield, bp 61–62° (45 mm) [lit. bp 65–67° (50 mm)].

Ethyl 1-(2-Thienyl)ethyl Ethyl Ether.—To a solution of 18.9 g (0.15 mol) of 2-acetylthiophene (Aldrich) dissolved in 100 ml of absolute ethanol at 0° was added 2.83 g (0.075 mol) of sodium borohydride. The solution was stirred at 0° for 0.5 hr and then at room temperature for 8.5 hr. The solution was acidified to

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[35] Y. K. Yur'ev and D. Eckhardt, *Zh. Obshch. Khim.*, **31**, 3274 (1961); *Chem. Abstr.*, **57**, 4622*a* (1962).

[36] W. Emerson and T. Patrick, Jr., "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 980.

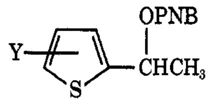
TABLE V

PROPERTIES OF SUBSTITUTED 1-(2-THIENYL)ETHYL p-NITROBENZOATES

Compd	Mp, °C	Calcd, %				Found, %			
		C	H	N	S	C	H	N	S
X = 5-OMe	66.8–67.6	54.72	4.26			54.66	4.18		
X = 5-c-C_3H_5	Oil								
X = 5-Me	48.5–49.0	57.72	4.50		11.01	57.53	4.70		11.05
X = 5-Ph	73.5–74.0	64.55	4.25			64.70	4.19		
X = H	64.5–65.8	56.31	4.00	5.05	11.56	56.33	4.24	5.06	11.50
X = 5-Br	99.0–100	43.80	2.81	(Br, 22.45)		43.68	2.95	(Br, 22.68)	
X = 4-Br	60.0–60.5	43.80	2.81	(Br, 22.45)		44.06	2.66	(Br, 22.24)	
X = 4,5-Br_2	99.0–99.7	35.88	2.08	(Br, 36.75)		35.82	2.25	(Br, 36.90)	
X = 4-COOEt	115.7–116.0	55.00	4.33			54.92	4.35		
X = 5-COOEt	91.5–92.0	55.00	4.33			55.22	4.15		

TABLE VI

EXPERIMENTAL RATE CONSTANTS FOR THE SOLVOLYSIS OF SUBSTITUTED 1-(2-THIENYL)ETHYL p-NITROBENZOATES IN 80% ETHANOL



Y	Temp, °C	Method[a]	k_1, sec^{-1}
5-Methoxy	13.40	Uv	$6.73 \pm 0.06 \times 10^{-2}$
	13.45	Uv	$7.19 \pm 0.23 \times 10^{-2}$
	13.45	Uv	$6.88 \pm 0.08 \times 10^{-2}$
	13.50	Uv	$6.97 \pm 0.04 \times 10^{-2}$
	13.50	Uv	$6.80 \pm 0.02 \times 10^{-2}$
	13.50	Uv	$6.57 \pm 0.08 \times 10^{-2}$
	0	PH-Stat	$7.74 \pm 0.15 \times 10^{-3}$
	0	pH-Stat	$8.51 \pm 0.17 \times 10^{-3}$
5-Cyclopropyl	25.00	T	$1.15 \pm 0.003 \times 10^{-3}$
	25.00	T	$1.13 \pm 0.004 \times 10^{-3}$
5-Methyl	44.63	Uv	$1.62 \pm 0.04 \times 10^{-3}$
	44.63	Uv	$1.36 \pm 0.06 \times 10^{-3}$
	45.00	T	$1.32 \pm 0.07 \times 10^{-3}$
	45.07	T	$1.70 \pm 0.03 \times 10^{-3}$
	25.00	Uv	$2.39 \pm 0.02 \times 10^{-4}$
	25.00	Uv	$1.93 \pm 0.01 \times 10^{-4}$
	25.00	T	$1.78 \pm 0.02 \times 10^{-4}$
	24.98	T	$1.83 \pm 0.02 \times 10^{-4}$
	24.98	T	$1.81 \pm 0.02 \times 10^{-4}$
5-Phenyl	45.00	Uv	$4.98 \pm 0.28 \times 10^{-4}$
	45.00	Uv	$5.14 \pm 0.33 \times 10^{-4}$
	45.00	Uv	$5.02 \pm 0.21 \times 10^{-4}$
	45.06	T	$4.81 \pm 0.05 \times 10^{-4}$
	24.98	T	$3.23 \pm 0.18 \times 10^{-5}$
	24.98	T	$3.77 \pm 0.15 \times 10^{-5}$
Hydrogen	45.00	T	$2.61 \pm 0.05 \times 10^{-5}$
	25.00	T	$2.27 \pm 0.04 \times 10^{-6}$
5-Bromo	75.00	T	$1.14 \pm 0.03 \times 10^{-4}$
	75.00	T	$1.18 \pm 0.02 \times 10^{-4}$
	44.93	T	$4.31 \pm 0.14 \times 10^{-6}$
	45.00	T	$3.97 \pm 0.10 \times 10^{-6}$
4-Bromo	75.00	T	$6.55 \pm 0.23 \times 10^{-6}$
	60.00	T	$9.12 \pm 0.53 \times 10^{-7}$
4,5-Dibromo	89.66	T	$1.29 \pm 0.04 \times 10^{-5}$
	75.00	T	$2.24 \pm 0.09 \times 10^{-6}$
4-Ethoxy-carbonyl	89.66	T	$1.57 \pm 0.02 \times 10^{-5}$
	75.00	T	$2.59 \pm 0.08 \times 10^{-6}$
	75.00	T	$2.68 \pm 0.08 \times 10^{-6}$
5-Ethoxy-carbonyl	110.00	T	$1.18 \pm 0.03 \times 10^{-5}$
	89.80	T	$1.47 \pm 0.09 \times 10^{-6}$

[a] T = trimetric.

a pH of 2 with 2 N hydrochloric acid and then was refluxed overnight. The resulting yellow solution and white solid was poured into 1 l. of water which was extracted with 3 × 100 ml of ether. The ether extracts were dried (magnesium sulfate), and the ether was stripped off under vacuum at room temperature to give 21.1 g (90%) of a pale yellow oil. Analysis by nmr revealed only traces of 2-vinylthiophene. Fractional distillation gave 17.0 g of pure ethyl 1-(2-thienyl)ethyl ether, bp 93–93.5° (40 mm) [lit.[37] bp 78–79° (16 mm)].

Product Analysis.—Analysis of the products from the solvolysis of 1-(2-thienyl)ethyl p-nitrobenzoate in 80% aqueous ethanol at 60° was carried out by an adaptation of the glpc procedure of Buckson and Smith,[38] who analyzed the ethanolysis products from phenyldimethylcarbinyl chloride and the corresponding p-nitrobenzoate. Additional confirmatory data was provided by nmr spectroscopy.

1-(2-Thienyl)ethyl p-nitrobenzoate (0.015 M) in 80% ethanol was solvolyzed at 60° for 18 hr (*ca.* 10 half-lives). The solution was diluted with water and extracted with 6 × 50 ml of dichloromethane. The combined organic extracts were washed with 50 ml of saturated sodium bicarbonate solution and 50 ml of water. After drying over anhydrous magnesium sulfate, the solution was filtered and then concentrated to *ca.* 5 ml by distilling the solvent through a 12-in. Vigreux column.

A portion (10 μl) of the remaining solution was injected into an Aerograph A90-P gas chromatograph equipped with a 5 ft × 0.25 in. 10% Carbowax on Chromosorb W column which had been treated with KOH. The column and injection port were kept at 114 and 147°, respectively. Ethyl 1-(thienyl)ethyl ether, 2-vinylthiophene, and 1-(2-thienyl)ethanol were shown to be completely stable under these conditions. The molar responses of the ether, alcohol, and 2-vinylthiophene were determined in separate experiments. In a control experiment a solution of the three compounds was subjected to the analysis procedure and the composition of the mixture was shown to be unchanged. In a separate experiment it was shown that 3% of 2-vinylthiophene could be observed in a mixture. Analysis of the solvolysis products and correcting for the molar responses showed the products to be 82 ± 10% ethyl 1-(2-thienyl)ethyl ether and 18 ± 10% 1-(2-thienyl)ethanol. No peak due to 2-vinylthiophene could be observed.

As an additional check on the nature of the solvolysis products the dichloromethane solution of the solvolysis products was examined with a Varian HA-100 nmr spectrometer. A quartet at δ 3.3 which could be assigned to the $-OCH_2CH_3$ methylene group of the ether product was clearly visible. Two superimposed doublets at δ 1.4 which could be assigned to the carbinyl methyl groups of the alcohol and ether were also observed. By integrating these peaks it was calculated that the solvolysis product consisted of 75 ± 10 mol % of the ether product and 25 ± 10 mol % of the alcohol product. No trace of the largest vinyl hydrogen peak in 2-vinylthiophene, which occurs at δ 5.8, could be observed.

Kinetic Procedures.—The kinetic solutions were prepared to be *ca.* 0.013 M p-nitrobenzoate in 80% aqueous ethanol. The solvent was prepared by mixing four parts of ethanol with one part of water by volume. The ethanol was purified by distilling commercial absolute ethanol twice from iodine-activated magnesium according to the method of Lund and Bjerrum.[39] The ethanol contained less than 0.05% water as determined by titration with Karl Fisher reagent. The water was laboratory distilled water. The volumes of the liquids were measured in pipettes and mixed at room temperature.

The kinetic samples were prepared by weighing 0.0013 mol

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(37) W. Emerson and T. Patrick, Jr., *J. Org. Chem.*, **13**, 729 (1948).

(38) R. L. Buckson and S. G. Smith, *ibid.*, **32**, 634 (1967).

(39) M. Lund and J. Bjerrum, *Ber.*, **64**, 210 (1931).

p-nitrobenzoate ester and dissolving the ester in 80 ml of absolute ethanol. For the faster runs this ethanol solution was thermostated in a volumetric flask in the temperature bath. To the thermostated solution was added 20 ml of distilled water at temperature, and, after temperature equilibration, aliquots were removed for titration. For the slower runs requiring higher temperatures, a sealed ampoule technique was used.

The aliquots from the kinetic runs were quenched in absolute ethanol and the liberated *p*-nitrobenzoic acid was titrated with *ca.* 0.0075 *M* potassium hydroxide in absolute ethanol on a Metrohm Potentiograph E336-A automatic recording titrator using the first derivative curve.

The solvolysis of 1-(5-methoxy-2-thienyl)ethyl *p*-nitrobenzoate at 13.5° was too rapid to be followed by the titration procedure. Instead an ultraviolet spectrophotometric procedure was used. The ultraviolet spectrum of the ester changed in a first-order manner to that of the reaction products if a slight amount of sodium bicarbonate was present to keep the liberated *p*-nitrobenzoic acid as the anion. A Gilford Model 2000 automatic recording spectrophotometer was used to follow the progress of the reaction. Rates were determined by both the ultraviolet spectrophotometric and titrimetric techniques for the 5-methyl and 5-phenyl compound under conditions which gave half-lives of 0.5 hr or less. The agreement in rates was quite satisfactory.

The rate of solvolysis of 1-(5-methoxy-2-thienyl)ethyl *p*-nitrobenzoate at 0.00° was slow enough to be followed by a titrimetric procedure. About 0.3 g of the ester was dissolved in 0.5 ml of dioxane. The dioxane solution was injected into 25 ml of 80% ethanol equilibrated at 0.00°. The solution was titrated with 0.66 *N* potassium hydroxide in 80% ethanol with a Radiometer SBR2 Titrigraph. The pH was kept constant at 7.6.

Measured rate constants are recorded in Table VI.

Registry No.—2-Acetyl-5-ethoxycarbonylthiophene, 33148-82-2.

Transmission of Substituent Effects in Heterocyclic Systems. The Solvolysis of Substituted 3-Furyl Derivatives[1]

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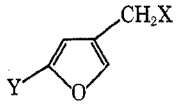
The rate of solvolysis of 2-(5-methyl-3-furyl)-2-propyl *p*-nitrobenzoate is substantially larger than the solvolysis rate for 2-(3-furyl)-2-propyl *p*-nitrobenzoate in 80% ethanol. The correlation of solvolysis rates for other 3-furyl systems is not satisfactory using pseudo meta relationships. However, generally useful and satisfactory correlations are obtained from consideration of CNDO/2 and INDO molecular orbital parameters for these systems. These parameters also provide an excellent basis foı additional predictions.

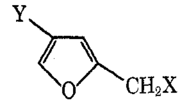
In a previous paper it has been shown that the solvolysis rates of a number of 5-substituted 1-(2-furyl)-ethanol derivatives are satisfactorily correlated by the Hammett relationship, using Brown's σ_p^+ substituent constants.[3] Notable was the high sensitivity of the furan ring to the electronic effect of the substituent in such a correlation, with ρ being -8. These observations were largely limited to 5-substituted 2-furyl systems, because of the generally difficult accessibility of β-substituted furans. The 5-Y-2-furyl relationship may be thought of as a normally "conjugating" relationship as exemplified by consideration of valence bond resonance structures.

It was of interest to extend these observations on the mode of transmission of substituent effects to "nonconjugating" relationships in the furan system. Such systems, A and B, pose some problems in synthesis; as a consequence, we have therefore obtained a somewhat limited amount of information. Nonetheless, the pattern which emerges is quite clear, and points to some particularly interesting general conclusions.

Yur'ev, Gal'bershtam, *et al.*,[4,5] have reported that the rate of methanolysis of 2,5-dimethyl-3-chloromethylfuran is 18 times that of 2-methyl-3-chloromethylfuran. This striking rate increase for introduction of a methyl group in a "nonconjugating" position (*i.e.*, position 5) is unusual; it is to be contrasted with the effect of a methyl group introduced in the meta position in benzene systems. For benzyl systems $k_{m\text{-Me}}/k_H$ ratios are typically 2 or 3.[6]



A



B

Our results show that this high ratio is characteristic of the furan system, and is not a singular or fortuitous result, due perhaps to ortho substitution. We have observed similar high rate ratios in both simple secondary and tertiary systems. From the results given in Table I, for the secondary systems **1** and **2**, the rate ratio k_{Et}/k_H is 8.85; in the tertiary systems, **3** and **4**, the rate ratio k_{Me}/k_H is 6.0.

TABLE I

RATE CONSTANTS FOR SOLVOLYSIS OF SOME SUBSTITUTED FURAN DERIVATIVES IN 80% ETHANOL

Compound solvolyzed	Temp, °C	k, sec^{-1}
1-(3-Furyl)ethyl *p*-nitrobenzoate (**1**)	75.00	8.18×10^{-6}
1-(5-Ethyl-3-furyl)ethyl *p*-nitrobenzoate (**2**)	75.00	7.24×10^{-5}
2-(3-Furyl)-2-propyl	25.00	4.57×10^{-4}
p-nitrobenzoate (**3**)	25.00	4.66×10^{-4}
2-(5-Methyl-3-furyl)-2-propyl *p*-nitrobenzoate (**4**)	25.00	2.75×10^{-3}

A rational explanation of these observations comes

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[2] Graduate Fellow on the University of California–Chile Cooperative Program from funds provided by the Ford Foundation, 1966–1970.

[3] D. S. Noyce and G. V. Kaiser, *J. Org. Chem.*, **34**, 1008 (1969).

[4] Y. K. Yur'ev, M. A. Gal'bershtam, and A. F. Prokof'eva, *Izv. Vyssh. Ucheb. Zaved., Khim. Khim. Tekhnol.*, **7**, 598 (1964); *Chem. Abstr.*, **62**, 3897*i* (1965).

[5] M. A. Gal'bershtam, G. T. Khachaturova, N. E. Bairamova, K. Y. Novitskii, and Y. K. Yur'ev, *Izv. Vyssh. Ucheb. Zaved., Khim. Khim. Tekhnol.*, **11**, 1395 (1968); *Chem. Abstr.*, **71**, 21307b (1969).

[6] Exemplary are the following: cumyl chlorides, 2.0, 2.28 [Y. Okamoto, T. Inukai, and H. C. Brown, *J. Amer. Chem. Soc.*, **80**, 4972 (1958)]; benzhydryl chlorides, 2.1 [J. F. Norris and J. T. Blake, *ibid.*, **50**, 1808 (1928)]; benzyl tosylates, 2.65 [A. Streitwieser, *et al.*, *ibid.*, **92**, 5141 (1970)].