Transmission of Substituent Effects through Furan and Thiophen Rings. Rates of Reaction of Substituted 2-Benzoyl-furans and -thiophens with Sodium Borohydride

By **Mariella Fiorenza, Alfredo Ricci,*** and **Giuseppe Sbrana**, Istituto di Chimica Organica dell'Università, Centro di studio sulla chimica e la struttura dei composti eterociclici del C.N.R., Firenze, Italy
Graziella Pirazzini, Laboratorio dei Composti del Carbonio contenenti eteroatomi e loro applicazione, C.N.R., Via Tolara 89, 40064 Ozzano Emilia, Bologna, Italy
Colin Eaborn * and **John G. Stamper**, School of Molecular Sciences, University of Sussex, Brighton BN1 9QJ

Rates of reduction by sodium borohydride in propan-2-ol have been measured for the 2-furyl and 2-thienyl ketones 2-(XC_6H_4CO)C_4H_2YE (E = O or S) for a range of X groups with Y = H, and of Y groups with X = H. The results permit direct comparisons to be made of transmission of substituent effects through the various aromatic rings to the same reaction centre, and it is concluded that the substituent effects are transmitted to virtually identical extents through the two heterocyclic rings, but markedly less effectively through the benzene ring. Charge distributions have been calculated by an *ab initio* method for furan, thiophen, and benzene and for the carbanions, 2-furylCH_2^-, 2-thienylCH_2^-, and PhCH_2^-. The change in the π-electron density at the 5-position on introduction of the 2-CH_2^- groups is smaller for furan than for thiophen, and the change in the latter case is slightly smaller than that induced at the 4-position on introduction of the 1-CH_2^- group for benzene, suggesting that transmission of conjugative effects between *p*-positions in the benzene ring is greater than that between the 5- and 2-positions in the heterocyclic compounds. The corresponding changes in total electron density, however, are effectively the same for all three rings. The electron density on the CH_2^- group is virtually identical in all three carbanions, suggesting that, contrary to the usual assumption, the π-systems of furan and thiophen rings do not interact more readily than those of benzene with a substituent capable of conjugation. Some of the data have been used to derive $\sigma_{5,2}$ and $\sigma_{4,2}$ constants for thiophen and furan systems.

THERE has been much interest during the past 20 years in comparisons between substituent effects in heterocyclic systems and those in benzene derivatives.[1,2] While the study described below is concerned with the transmission of substituent effects from the 4- or 5- to the 2-position of thiophen or furan (referred to below as 4,2- and 5,2-interactions) compared with those from the 3- or 4- to the 1-position of benzene (3,1- and 4,1-interactions), it has general implications for transmission of substituent effects through other heterocyclic systems, and, indeed, through any system other than a single benzene ring.

It was suggested by Hammett in his original presentation of the Hammett equation that the effect of 4- and 5-substituents on reactions in side-chains at the 2-position of furan could be regarded as analogous to those of *m*- and *p*-substituents on reactions of benzene derivatives,[3] and use of σ_m and σ_p constants, respectively, for 4- and 5-substituents in furan and thiophen derivatives has commonly led to satisfactory linear correlations.[1,2] Furthermore, σ_p^+ constants can be satisfactorily used for 5-substituents in electrophilic substitution or formation

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[1] H. H. Jaffé and H. L. Jones, *Adv. Heterocyclic Chem.*, 1964, **3**, 209.

[2] P. Tomasik and C. D. Johnson, *Adv. Heterocyclic Chem.*, 1976, **20**, 1.

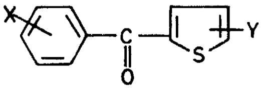
[3] L. P. Hammett, 'Physical Organic Chemistry,' McGraw-Hill, New York, 1940, ch. 7.

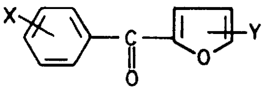
of side-chain carbonium ions at the 2-position of furan and thiophen derivatives.[2] The implication is that the balance of polar and conjugative effects of the substituents at the 5-position on reactions of 2-derivatives, which determines the 5,2-interaction, is the same as that implied for the 4,1-interaction in benzene systems by the σ_p (or, where appropriate, σ_p^+) constants. Similar remarks can be made about 4,2-interactions in the heterocyclic compounds and 3,1-interactions in benzene, but for simplicity we concentrate below mainly on comparison of the corresponding 5,2- and 4,1-interactions.

The question then arises of the relative magnitudes of the 5,2-effects for a range of substituted compounds compared with those of the corresponding 4,1-effects in benzene derivatives, usually referred to as the relative ease of transmission of substituent effects in the various systems. The common practice is to determine the ρ value for a particular reaction, *e.g.* the ionization of 5-X-2-furoic or -thiophen-2-carboxylic acids, by use of σ_p constants for the 5-X groups, and then to compare this value with that for the corresponding reaction in the benzene series, *e.g.* the ionization of benzoic acids.[1,2] Thus Exner and Jonas found the ρ values determined in this way for ionization of the acids p-$\mathrm{XCH_2C_6H_4CO_2H}$, 5-$\mathrm{XCH_2{\cdot}C_4H_2S{\cdot}CO_2H}$-2, and 5-$\mathrm{XCH_2{\cdot}C_4H_2O{\cdot}CO_2H}$-2 to be in the ratio 1 : 1.17 : 1.31, and those for ionization of the acids $\mathrm{XC_6H_4CO_2H}$, 5-$\mathrm{X{\cdot}C_4H_2S{\cdot}CO_2H}$-2, and 5-$\mathrm{X{\cdot}C_4H_2O{\cdot}CO_2H}$-2 to be in the fairly similar ratio 1 : 1.13 : 1.43.[4] They concluded that the increasing sensitivity to substituent effects reflected the increasing mobility of the electrons of the rings as the aromaticity decreases in the sequence benzene > thiophen > furan. Analogous observations were made, and similar conclusions reached, in studies of substituent effects on physical properties, *e.g.* the half-wave potentials of the nitro- and formyl-aromatic compounds,[5] or carbonyl stretching frequencies of the latter[6] and of 2-acetylthiophens,[7] although much bigger differences between the benzene and heterocyclic systems were found in those cases.

We suggest that such a procedure, while possibly leading in many cases to reasonably correct conclusions, is in principle invalid. This is because it involves the unjustifiable assumption that the intrinsic ρ value, which would be measured by the influence of a notional standard substituent the electronic effect of which is transmitted to a standard extent to the reaction centre, is the same for the reactions of the two heterocyclic and the benzene derivatives. In other words, it assumes that the change in the effective charge at the reaction centre on going from the reactant to the transition state (when free energies of activation are considered) or products (when overall free energy changes in an equilibrium are considered) is the same in all cases, and we can see no justification for this assumption. In a reaction the transition states could easily lie at different positions along the reaction co-ordinate in the various systems, and even if these positions are the same, differing degrees of interaction with a heteroatom or solvation may result in differences in the effective charges available to interact with the substituent. For an equilibrium in solution, not only may both the initial and final states differ slightly in one system from those in another, but differential solvation may also again be important. The same uncertainty is present even for correlations involving spectroscopic quantities; for example, it is, in principle, no more justifiable to assume that the intrinsic ρ values for variation of $\nu(\mathrm{C{=}O})$ are the same for $\mathrm{X{\cdot}C_4H_2O{\cdot}CHO}$ and $\mathrm{XC_6H_4CHO}$ compounds than to assume that they are the same for $\mathrm{XC_6H_4CHO}$ and $\mathrm{XC_6H_4COCH_3}$ compounds. One can conceive of the situation in which, in a given reaction, the effective change in charge at the reaction centre on going to the transition state is smaller for say, a thiophen system (with the reaction centre attached at the 2-position) than for the corresponding benzene system, but the interaction of the charge with a 5-substituent in the thiophen is correspondingly greater than that with p-substituent in the benzene system, so that by using σ_p constants for both systems we would arrive at the same ρ values for the two systems and wrongly conclude that the magnitude of the transmission of the substituent effects is the same in both cases.

In our view the problem can only be resolved experimentally by comparing the influences of substituents in a heterocyclic ring with those for substituents in the benzene ring acting on an identical reaction site.* Thus we have examined the behaviour of the 2-benzoylthiophen and -furan derivatives (I) and (II) and while, as discussed below, this is not an ideal system because of minor steric complications, it illustrates well the approach we advocate.


(I)


(II)

RESULTS AND DISCUSSION

The reaction we examined was the sodium borohydride reduction of the series of ketones (I) and (II) in propan-2-ol at 25 °C. This type of reduction has been much studied, and shows good kinetic behaviour and a fairly high sensitivity to substituent effects.[9,10] Our results

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* One of us used this type of approach 16 years ago to compare transmissions of substituent effects through fluorene and benzene rings,[8] but it has not previously been used in studies of the heterocyclic systems.

[4] O. Exner and J. Jonas, *Coll. Czech. Chem. Comm.*, 1964, **29**, 2016.

[5] A. Běno, A. Krutošiková, L. Fiševa, and R. Frimm, *Coll. Czech. Chem. Comm.*, 1973, **38**, 2734; A. Běno and A. Krutošiková, *ibid.*, 1977, **42**, 508.

[6] A. Pérjessy, R. Frimm, and P. Hrnčiar, *Coll. Czech. Chem. Comm.*, 1972, **37**, 3302.

[7] L. P. Pivovarevich, L. A. Kutulya, Yu. N. Surov, S. V. Tsukerman, and V. F. Lavrushin, *Khim. Geterotsikl. Soedinenii*, 1974, 918.

[8] C. Eaborn, R. C. Golesworthy, and M. N. Lilly, *J. Chem. Soc.*, 1961, 3052.

[9] H. C. Brown, O. H. Wheeler, and K. Ichikawa, *Tetrahedron*, 1957, **1**, 214.

[10] G. T. Bruce, A. R. Cooksey, and K. J. Morgan, *J. Chem. Soc.*, 1975, 551.

are shown in Table 1, which along with the observed rate constants, k_2, lists the values of k_{rel}, the rate constant relative to that of the parent compound (I) or (II) with X = Y = H.*

TABLE 1

Rates of reduction of the furyl and thienyl ketones 2-$(XC_6H_4CO)\cdot C_4H_2E\cdot Y$ (E = O or S) by sodium borohydride in propan-2-ol at 25 °C

No.	E	X	Y	k_2/l mol^{-1} s^{-1}	k_{rel}
1	S	*p*-OMe	H	6.03×10^{-5}	0.121
2		*p*-Me	H	1.48×10^{-4}	0.296
3		H	H	4.99×10^{-4}	1.0
4		*p*-Br	H	2.20×10^{-3}	4.4
5		*m*-Br	H	4.76×10^{-3}	0.95
6		*p*-NO_2	H	5.37×10^{-2}	1.08
7		H	5-OMe	2.44×10^{-5}	0.049
8		H	5-Me	1.07×10^{-4}	0.214
9		H	4-Me	2.94×10^{-4}	0.59
10		H	5-Br	4.76×10^{-3}	9.5
11		H	5-NO_2	2.28	4.6×10^3
12	O	*p*-OMe	H	5.03×10^{-4}	0.182
13		*p*-Me	H	1.13×10^{-3}	0.41
14		H	H	2.76×10^{-3}	1.0
15		*p*-Cl	H	1.15×10^{-2}	4.2
16		*p*-NO_2	H	1.85×10^{-1}	6.7
17		H	5-OMe	2.53×10^{-4}	0.092
18		H	5-Cl	1.66×10^{-2}	6.0
19		H	5-NO_2	3.98	1.44×10^3

For variation of the substituent X in the benzene ring of the thiophen derivatives (I) with Y = H, the log k_{rel} values give a good linear correlation with σ constants, with a slope, ρ, of 2.76 (correlation coefficient 0.998; intercept −0.08). A plot distinctly better in appearance, with ρ 2.58 (correlation coefficient 0.999; intercept 0.01) is obtained by use of the Yukawa–Tsuno equation. $\log k_{rel} = \rho[\sigma + r(\sigma^+ - \sigma)]$, with an r value of 0.2 (Figure 1). These results closely parallel those for the acetophenones XC_6H_4COMe (at 30 °C), which give a satisfactory plot against σ, but a better plot (ρ 2.7) if the Yukawa–Tsuno equation, with r 0.28, is used.[10] [The apparent difference in the r values in the two systems cannot be regarded as real, since a plot of log k for the acetophenones against log k for compounds (I) having Y = H and X varying, is linear well within the limits of accuracy of the rather scattered data for the former series. For the acetophenones, there is not very good agreement between the rate constants or even k_{rel} values determined by Bowden and Hardy [11] and those determined by Bruce *et al.*[10]]

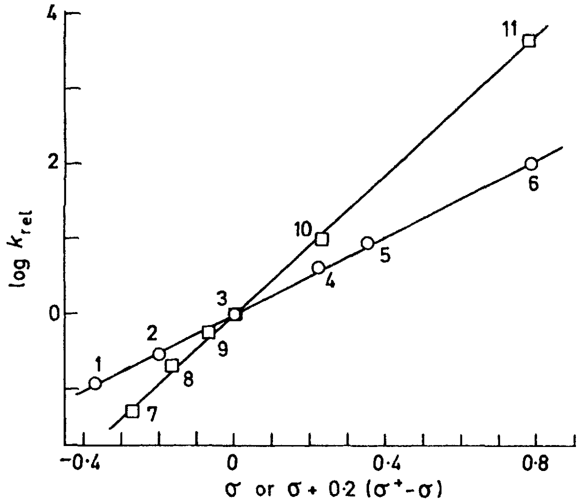

FIGURE 1 Plots of log k_{rel} (i) against $[\sigma + 0.2(\sigma^+ - \sigma)]$ for varying X in $XC_6H_4CO\cdot C_4H_3S$ (circles), and (ii) against σ for varying Y in $PhCO\cdot C_4H_2S\cdot Y$ (squares). For numbering of points see Table 1

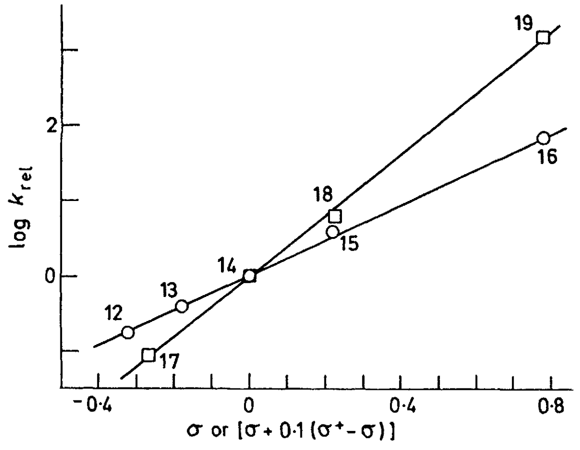

FIGURE 2 Plots of log k_{rel} (i) against $[\sigma + 0.1(\sigma^+ - \sigma)]$ for varying X in $XC_6H_4CO\cdot C_4H_3O$ (circles), and (ii) against σ for varying Y in $PhCO\cdot C_4H_2O\cdot Y$ (squares). For numbering of points see Table 1

For variation of Y in the ketones (I) with X = H, including one 4-substituent (Me) for which the σ_m constant is used, the plot of log k_{rel} against σ is an excellent straight line (Figure 1), with a slope of 4.64 (correlation coefficient 0.999; intercept −0.02). In this case use of the Yukawa–Tsuno equation does not improve the correlation.

Similar plots are given by the data for the furan derivatives (II). Again, for variation in X with Y = H the correlation of log k_{rel} with σ is very good, with ρ 2.42 (correlation coefficient 0.998; intercept −0.10), and a still better plot, with ρ 2.35 (correlation coefficient 0.999; intercept −0.02) is obtained by use of the Yukawa–Tsuno equation with r 0.1 (Figure 2); with r 0.2, the correlation (ρ 2.27; correlation coefficient 0.998; intercent 0.075) is similar in precision to that for r 0. [The difference, between the best r value for the thiophen and furan ketones is not significant, and a plot of log k_{rel} for varying X in (II) with Y = H against log k_{rel} for varying X in (I) with Y = H is an excellent straight line (slope 0.87; correlation coefficient 0.9995; intercept 0.05).] For variation of Y with X = H, correlation with σ is

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* For reaction of benzophenone with sodium borohydride in propan-2-ol at 25 °C, Brown and his colleagues observed a value of $10^4 k_2$ of 15.8 l mol^{-1} s^{-1},[9] which lies midway between our values for 2-benzoyl-thiophen (5.02) and -furan (27.5). A corresponding sequence of reactivity was observed for the reduction of the compounds $PhCOCH_3$, 2-$C_4H_3S\cdot COCH_3$, and 2-$C_4H_3O\cdot COCH_3$,[10] and on the simplest assumptions, neglecting any steric and solvation differences, the results imply that relative to the phenyl group the 2-thienyl group releases and the 2-furyl group withdraws electrons from the carbonyl group.

[11] K. Bowden and M. Hardy, *Tetrahedron*, 1966, **22**, 1169.

excellent, with ρ 4.01 (correlation coefficient 0.999; intercept −0.015) (Figure 2).

It is clear from the results that 4- or 5-substituents, Y, in the heterocyclic rings have substantially greater effects on the rate than do the corresponding *m*- or *p*-substituents, X, in the benzene rings, and thus that the transmission of substituent effects through the furan and thiophen rings is, indeed, greater than that through the benzene ring. At first sight it might also appear from the respective ρ values, or from direct comparison of the effects of substituents in the two systems, that the transmission is greater through the thiophen than through the furan ring, but when allowance is made for the difference in the intrinsic ρ values in the two systems, as indicated by the ρ values for variation of X with Y = H, the magnitudes of the transmission through the furan and thiophen rings can be seen to be virtually identical. This can be illustrated in several ways. For example, the ratio of the ρ value for the plots against σ given by the Y to that given by the X substituents is 4.64 : 2.76, *i.e.* 1.68, for the thiophen derivatives and 4.01 : 2.35, *i.e.* 1.66, for the furan derivatives. However, it is better to avoid the assumptions inherent in the use of σ constants, and make direct comparison of the rates for corresponding compounds; thus a plot of log k_{rel} for the (4- or) 5-substituted thiophen derivatives (I; X = H) against log k_{rel} for the corresponding (*m*- or) *p*-substituted compounds (Y = H) has a slope of 1.68 (correlation coefficient 0.997), while the analogous plot for the furan derivatives (II) has a slope of 1.65 (correlation coefficient 0.995). Most impressive of all, a single line, with a slope of 1.67, suffices for both series when the values of log k_{rel} for varying Y are plotted against those of log k_{rel} for varying X (correlation coefficient 0.995). (It is noteworthy that in this last case there is a very good linear correlation when the points for the nitro-substituents are omitted; slope 1.40; correlation coefficient 0.998; intercept 0.00.) The results thus nicely illustrate our contention that it is unsafe to equate the relative ρ values for the several corresponding aromatic systems with the ease of transmission of the substituent effects. If the usual reasoning were followed, the ρ values obtained on varying Y while keeping X = H constant would be taken to imply that the transmission through the thiophen is greater than that through the furan ring, which would be incorrect. Direct comparison of ρ values in analogous thiophen and furan analogues, has, in fact, usually indicated that transmission is somewhat greater for furan.[1,2,4-7]

Transmission of substituent effects through the thiophen and benzene systems can also be compared by examination of the carbonyl stretching frequencies of compounds (I) (Table 2). [This is not possible with the furan series (II), because of broadening or twinning of the carbonyl bands, as mentioned below.] A plot of ν(C=O) against σ^+ constants for varying X (with Y = H) is a very good straight line, of slope 6.5 (correlation coefficient 0.998). A similar plot for varying Y (with X = H), using $\sigma_p{}^+$ and $\sigma_m{}^+$ constants for 5- and 4-Y substituents, respectively, gives a slightly less satisfactory straight line of slope 13.2 (correlation coefficient 0.992). Again the transmission is substantially greater through the thiophen than through the benzene ring, the ratio of the ρ values being 2.0, compared with 1.7 for the borohydride reduction.

We have mentioned that the system we used is not ideal. This is because there are two possible complications arising from steric effects, *viz.* (a) the non-planarity of the compounds (I) and (II), and (b) the existence of *cis*- and *trans*-rotational isomers in solutions of (I) and (II). We shall show that these complications are unlikely to be of major significance.

TABLE 2

Carbonyl stretching frequencies in the thienyl ketones $(2\text{-}XC_6H_4CO)\cdot C_4H_2S\cdot Y$

H	*p*-OMe	*p*-Me	H	*p*-Br	*m*-Br	*p*-NO$_2$	H	H	H	H
Y	H	H	H	H	H	H	5-OMe	4-Me	5-Br	5-NO$_2$
ν(CO)/cm^{-1}	1 640.5	1 643.5	1 646	1 646.5	1 648.5	1 650.5	1 634	1 645	1 646	1 655

Dipole moment and n.m.r. studies show that 2-thienyl ketones of type (I) are not planar;[12] it is usually assumed that the twisting from the plane is markedly greater for the phenyl than for the thienyl group, since (it is argued) conjugation with the carbonyl group would be expected to be poorer for the more aromatic benzene ring, and on this basis the torsion angle for the twisting about the $2\text{-}C_4H_3S\cdot CO\text{–}Ph$ bond was estimated to be *ca.* 30—40°.[12] It could thus be argued that conjugative effects between the phenyl and carbonyl groups in (I) and (II) may be abnormally low, so that use of the ρ values given by varying X will imply artificially large degrees of transmission through the thiophen and furan rings. This can, however, be ruled out as a major influence. First, we note that the ρ values for varying X with Y = H in ketones (I) and (II), *viz.* 2.6 and 2.3, respectively, are rather close to that for the $XC_6H_4COCH_3$ series, *viz.* 2.7 (the Yukawa–Tsuno equation with *r* 0.2 being used throughout); since the rate constants for all three parent compounds are fairly similar, this is consistent with a normal interaction between the benzene rings and the carbonyl group in compounds (I) and (II). Furthermore, a ρ value of 2.65 applies also to substituted fluorenones,[13] in which the rings are constrained into planarity with the carbonyl group. [Fluorenone is about three times as reactive as ketone (II) with X = Y = H.] Secondly, as we have seen, the effects of groups X in the ketones (I) and (II) with Y = H, correlate very well with those in the acetophenones $XC_6H_4COCH_3$, so there is no distor-

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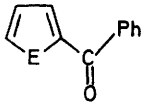
[12] C. Andrieu, D. Bertin, and H. Lambroso, *Compt. rend.*, 1965, **260**, 131; C. Andrieu, M. L. Martin, and G. J. Martin, *Bull. Soc. chim. France*, 1968, 703; M. L. Martin, C. Andrieu, and G. J. Martin, *ibid.*, p. 698.

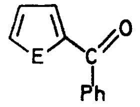
[13] C. G. Smith and R. P. Bayer, *Tetrahedron*, 1962, **18**, 323.

tion of the balance of polar and conjugative effects of the X groups in the reactions of (I) and (II); thus there can be no serious consequence of departure from coplanarity of the benzene ring and carbonyl group.* Finally, for variation of X in (I) with Y = H, there is a very good correlation between ν(C=O) and σ^+, as is the case for substituted acetophenones,[15] the need to use σ^+ constants arising from the importance of the direct conjugation between the X groups and the carbonyl groups. The implication is that even when conjugative effects are especially important there is no distortion of the overall effects of the X substituent in compounds (I), and thus no serious interference with the transmission of the effects of these groups.

Even if departure from coplanarity does cause some small reduction in the transmission of substituent influences through the benzene rings in compounds (I) and (II), it is most unlikely that the effect would differ much between (I) and (II), so that the comparison of transmission through the furan and thiophen rings would be unaffected. There is however, an additional complication, arising from the fact that both *syn*- and *anti*-conformers [as in (III) and (IV)] can be present in solutions of 2-furyl and 2-thienyl ketones. (For leading references see ref. 16.) The *syn*-conformer is usually strongly favoured for the thiophen derivatives, but with furan derivatives a substantial proportion of the *anti*-conformer is often present, and, indeed, appears greatly to predominate for 2-acetylfuran in cyclohexane.[16] The equilibria are strongly dependent on the medium, and polar solvents favour the *syn*-form. The broadening or doubling of the carbonyl bands of the furyl ketones (II) is attributable to the presence of the two conformers,[15,17] and the appearance of single bands for the thienyl ketones (I) suggests that little of the *anti*-form is present. However, for both (I) and (II) it is likely that significant amounts of both conformers are present, and that these are rapidly interconverted. The reaction will then proceed very predominantly through the less stable conformer, and this is likely to be the same one for (I) and (II), so that the observed ρ values are directly comparable. Alternatively, in each case the forms (III) and (IV) may react at comparable rates, but they would then be expected to give rise to very similar ρ values, with the weighted average of ρ not differing significantly from the separate values. Thus it is unlikely that the existence of the conformers casts doubt on our conclusion that the effectiveness of the transmission is much the same for the two heterocyclic rings.



(III) (*syn*)



(IV) (*anti*)

Other Approaches.—There are other ways of making comparisons of substituent effects in various systems. Johnson and his colleagues prefer to interpret differences between ρ values in, say, benzene, furan, and thiophen systems 'as representing non-additivity of substituent effects, the heteroatom being taken as a substituent replacing ·CH:CH· in a benzenoid ring and being able on occasion to interact *via* proximity effects with the side chain, altering its susceptibility to substituent influences.'[2,18] This is a valid procedure for examining the concept of additivity, and, indeed, the principle involved is closely related to our view that intrinsic ρ values cannot be assumed to be the same in corresponding systems, but it gives little help in interpreting the differences between observed ρ values in the various systems.

The approach adopted by Butler is to use the Dewar–Grisdale treatment[19] (see below) to calculate σ values associated with 4,2- and 5,2-interactions.[20] For the thiophen system this gives a set of σ values which agrees with that derived from the ionization of the acids 4- and 5-$XC_4H_2S{\cdot}CO_2H$-2 in various media on the assumption that the ρ value is the same as that for the benzoic acids under the same conditions. Thus the calculated σ values are (numerically) generally slightly larger than those for benzene derivatives, indicating that the transmission of effects is slightly greater through the thiophen system. (To the extent that the calculated σ values agree with those derived experimentally by assuming the ρ values to be the same for the thiophen and benzene systems, the conclusion is exactly that which would be reached by directly comparing the ρ values obtained by using σ_m and σ_p values for the thiophen system.) We discuss below the results of more extensive calculations following the Dewar–Grisdale treatment.

We should point out that in our view it is unsatisfactory to test the validity of calculated σ values by assuming that the intrinsic ρ values are always the same in the thiophen or other system as in the corresponding benzene system; the approach we advocate above, involving comparisons of interactions of two different ring systems with the same reaction centre, is preferable. We further note that if calculations of σ constants are coupled with the assumption that intrinsic ρ values *are* always the same in a heterocyclic as in a benzene system, then the observed ρ values when σ_m and σ_p constants are used for

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* Substituent effects are somewhat more complex for substituted fluorenones because the electronic effects are transmitted to some extent through the unsubstituted ring.[13,14] However, the correlation with σ values for 2- and 3-substituted compounds is quite good, and use of an *r* value of 0.1 puts the point for the 3-OMe (equivalent to a *p*-OMe) group on the line. Thus even for these planar ketones the behaviour closely parallels that of the ketones (I) and (II).

[14] J. A. Parry and K. D. Warren, *J. Chem. Soc.*, 1965, 4049.

[15] P. J. Krueger, *Canad. J. Chem.*, 1973, **51**, 1363; see also M. Berthelot and C. Laurance, *ibid.*, 1975, **53**, 993.

[16] C. L. Cheng, I. G. John, G. L. D. Ritchie, P. H. Gore, and L. Farnell, *J.C.S. Perkin II*, 1975, 744.

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[18] C. D. Johnson, 'The Hammett Equation,' Cambridge University Press, Cambridge, 1973, p. 107.

[19] M. J. S. Dewar and P. J. Grisdale, *J. Amer. Chem. Soc.*, 1962, **84**, 3548.

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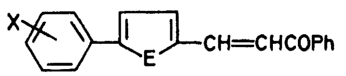
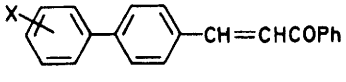
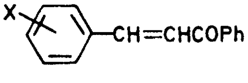
both systems should be in the same ratio for all appropriate reactions, which is not the case. For example, ρ values have been obtained for reactions of 5-substituted furoic acids and their ethyl esters by use of σ_p constants; the ratio of the ρ values to those for the corresponding benzoic acid systems are 1.4, 1.2, and 1.0, respectively, for (a) dissociation of the acid, (b) base hydrolysis of the ethyl esters, and (c) reactions of the acids with diazodiphenylmethane.[21]



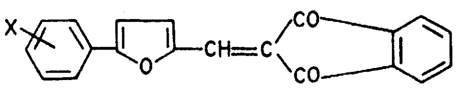
(V) E = O
(VI) E = S



(VII)



(VIII)



(IX)

The assumption that intrinsic ρ values are the same in corresponding systems is likely to be more accurate when the structural variations are remote from the ‘ reaction ’ site. For example, Perjéssy and his colleagues have examined the effects of substituents on the carbonyl stretching frequencies in the systems (V)—(VIII).[22] For both *cis*- and *trans*-isomers, in all cases plots of ν(C=O) against σ_m^+ and σ_p^+ constants give good straight lines. The intrinsic ρ value can reasonably be assumed to be virtually the same in all cases, and so the comparison of the observed ρ values should indicate the relative effectiveness of transmission of effects through the heterocyclic rings; they suggest transmission factors of 0.64, 0.44, and 0.27 for furan, thiophen, and benzene, respectively. Analogous use of compounds such as (IX) also indicates that transmission is about twice as effective through the furan as through the benzene ring.[23] The substantially greater transmission through the heterocyclic rings than through benzene is consistent with our results. The greater transmission through furan than through thiophen contrasts with our observations, but it cannot be assumed that the transmission factors will necessarily be in the same ratio for situations in which σ constants apply as for those in which σ^+ constants apply, since different blends of polar and conjugative effects are involved. We must also note that departure from coplanarity of the aromatic rings in compounds (V)—(VII) may cast some doubt on comparison of ρ values, but this cannot be a major effect since the correlations with σ^+ constants imply that there is good conjugation between the rings.

The results for systems of type (V)—(IX) do, incidentally, reinforce previously expressed doubts [24] about the reliability of the Dewar–Grisdale type of treatment, since it is most unlikely that the balance of field and resonance effects, as defined by Dewar and Grisdale, would remain constant for ketones (V)—(IX) and acetophenones, as is implied by the good applicability of σ^+ constants to all the systems.

ab initio *Calculations*.—We have carried out some *ab initio* calculations in an attempt to throw light on the question of the relative ease of transmission of substituent effects in furan, thiophen, and benzene. In spite of our doubts about its general validity, we use the Dewar–Grisdale approach to provide a conventional

TABLE 3

Charge distribution in ArH and $ArCH_2^-$

		In ArH			In $PhCH_2^-$ or $5\text{-}C_4H_3ECH_2^-$			Charge change		
ArH	Position	σ	π	Total	σ	π	Total	σ	π	Total
Furan	1 [a]	−0.52	+0.32	−0.20	−0.50	+0.23	−0.27	+0.02	−0.09	−0.07
Thiophen	1 [a]	−0.01	+0.28	+0.27	−0.05	+0.17	+0.12	−0.04	−0.11	−0.15
Furan	2	+0.14	−0.09	+0.05	+0.21	−0.25	−0.04	+0.07	−0.16 [b]	−0.09
Thiophen	2	−0.10	−0.08	−0.18	+0.02	−0.29	−0.27	+0.12	−0.20 [c]	−0.09
Benzene	*p*	−0.06	0.00	−0.06	+0.06	−0.22	−0.16	+0.12	−0.22 [d]	−0.10
Furan	3	−0.03	−0.07	−0.10	−0.07	−0.05	−0.12	−0.04	+0.02	−0.02
Thiophen	3	−0.03	−0.05	−0.08	−0.08	−0.01	−0.09	−0.05	+0.04	−0.01
Benzene	*m*	−0.06	0.00	−0.06	−0.08	0.00	−0.08	−0.02	0.00	−0.02
Furan	4	−0.03	−0.07	−0.10	+0.13	−0.36	−0.23	+0.16	−0.29	−0.13
Thiophen	4	−0.03	−0.05	−0.08	+0.13	−0.35	−0.22	+0.16	−0.30	−0.14
Benzene	*o*	−0.06	0.00	−0.06	+0.02	−0.16	−0.14	+0.08	−0.16	−0.08
Furan	5	+0.14	−0.09	+0.05	+0.06	+0.06	+0.12	−0.08	+0.15	+0.07
Thiophen	5	−0.10	−0.08	−0.18	−0.15	+0.06	−0.09	−0.05	+0.14	+0.09
Benzene	1	−0.06	0.00	−0.06	−0.11	+0.11	0.00	−0.05	+0.11	+0.06
Furan	CH_2^-				+0.15	−0.50	−0.35			
Thiophen	CH_2^-				+0.14	−0.46	−0.32			
Benzene	CH_2^-				+0.13	−0.45	−0.32			

[a] It is assumed that two units of nuclear charge are associated with the π-electrons for the oxygen and four for the sulphur atom. [b] To third place of decimals, −0.164. [c] To third place of decimals, −0.205. [d] To third place of decimals, −0.216.

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[21] W. K. Kwok, R. A. More O'Ferrall, and S. I. Miller, *Tetrahedron*, 1964, **20**, 1913.

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[23] A. Perjéssy, P. Hrnčiar, and A. Krutošiková, *Tetrahedron*, 1972, **28**, 1025.

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framework for the comparisons, and thus take the CH_2^- group as a model for substituents which interact conjugatively with the aromatic rings.[19]

In Table 3 we show the charge distributions in the parent ArH compounds and in the corresponding anions $ArCH_2^-$ for Ar = furyl, thienyl, and phenyl, given by minimum basis set (STO-3G) *ab initio* calculations using the Gaussian 70 package.[25] Experimental geometries [26] for thiophen and furan rings were used throughout, and the geometry of the CH_2^- group was taken as C–C, 1.43 Å; C–H, 1.12 Å; $H\widehat{C}H$, 114.5°, as given by optimization for furan. (Optimization for $PhCH_2^-$ gave a value of $H\widehat{C}H$ of 118°, and charge distributions not significantly different from those in Table 3.)

Some interesting features are evident. (a) The changes in the total charge induced at the 2-position of the furan and thiophen ring by the 5-CH_2^--substituent are effectively identical, and the same as the change induced at the 4-position of benzene by the 1-CH_2^--substituent. Since both the polar and conjugative effects of the CH_2^- group contribute to these changes in total charge density, the changes could reasonably be expected to offer a guide to the overall effect of 5- or *para*-substituents on reaction centres attached to the 2-position of the heterocyclics or 4-position of benzene, and suggest that there is no significant difference between the 5,2-interactions in furan and thiophen and the 4,1-interaction in benzene.

The smallness of the calculated changes in these total charges is of interest. It results from a compensation of the substantial increase in π-electron densities at the 2-positions of the heterocyclics or the 4-position of benzene by a marked decrease in the σ-electron densities at these positions. This can be associated with repulsion of nearby σ-electrons by the excess of π-electron density, and illustrates the weakness of the assumption that polar and conjugative effects can be treated as wholly separate, which is necessary in simple treatments of the Dewar–Grisdale type.

(b) The change in the π-charge induced at the 2-position by a 5-CH_2^- substituent, which in the Dewar–Grisdale approach provides a measure of the conjugative 5,2-interaction, is −0.164 for furan and −0.205 for thiophen, compared with a value of −0.216 for the 4-position in $PhCH_2^-$. On this indication, the 5,2-conjugation in the heterocyclics is less effective than the 4,1-conjugation in benzene.

(c) The π-electron (and total electron) densities on the CH_2^- group are virtually identical in all three $ArCH_2^-$ ions, which casts doubt on the usual assumption (see, *e.g.* refs. 5, 12, and 27) that the π-system for furan or thiophen, which are less aromatic, interacts markedly more effectively with conjugating substituents than does that of benzene.

(d) The change in either the π- or total-electron density induced by the 5-CH_2^- group is significantly greater for the nearby 4-position than for the 2-positions of the heterocyclic compounds, suggesting that a 5-substituent will give markedly larger effects at the 4- than at the 2-positions in these systems.

We can use the calculated values of the π-electron densities at the 2-positions of the 5-furyl- and -thienyl-CH_2^- anions and at the 4-position of $PhCH_2^-$ to provide measures of the $q_{i.j}$ values for use in the Dewar–Grisdale equation $\sigma_{i.j} = F/r_{i.j} + M/q_{i.j}$, where $\sigma_{i.j}$ is the substituent constant for a substituent at position i acting on position j, F a measure of the field set up by the substituent, $r_{i.j}$ the distance between atoms i and j, and M a measure of the combined π-inductive mesomeric effect of the substituent.[19] To derive the values of $q_{5.2}$ for furan and thiophen from the calculated change in π-charge densities at the 2-position on introduction of a 5-CH_2^- group, *viz.* −0.164 and −0.205, we multiply by the factor of −0.143 : 0.216 which 'normalizes' the π-charge change of −0.216 for the 4-position of $PhCH_2^-$ to match the Dewar and Grisdale's value of 1/7 for the $q_{4.1}$ value for benzene. This gives $q_{5.2}$ values of 0.109 and 0.136, respectively, for furan and thiophen. The values of $q_{4.2}$ for the heterocyclics are taken to be zero, as for the $q_{3.1}$ value for benzene. The $r_{5.2}$ value, in units of C–C bond lengths in benzene, are 1.57 and 1.78 for furan and thiophen, and corresponding $r_{4.2}$ values are 1.56 and 1.64. The σ values calculated for some typical substituents, with the aid of these values used from the Dewar–Grisdale equation given above are shown in Table 4, and the following features are noteworthy.

TABLE 4

Calculated σ constants for effects of 5- or 4-substituents on the 2-position of furan or thiophen, and empirical σ_m and σ_p constants for benzene

Sub-stituent	Furan		Thiophen		Benzene	
	$\sigma_{5.2}$	$\sigma_{4.2}$	$\sigma_{5.2}$	$\sigma_{4.2}$	σ_p	σ_m
MeO	−0.15	0.13	−0.24	0.12	−0.27	0.12
Me	−0.16	−0.08	−0.17	−0.07	−0.17	−0.07
H	0.00	0.00	0.00	0.00	0.00	0.00
Cl	0.34	0.42	0.27	0.40	0.23	0.37
Br	0.35	0.44	0.28	0.41	0.23	0.39
NO_2	0.91	0.79	0.85	0.75	0.78	0.71

(a) The calculated σ constants for the thiophen system do not differ significantly from those given by Butler, who used values of 0.138 and 0.009 for $q_{5.2}$ and $q_{4.2}$, respectively. There is an excellent linear correlation between our calculated σ constants for the thiophen system and the corresponding σ_p or σ_m constants for benzene (correlation coefficients 0.999; intercept 0.015), with a slope of 1.05. The corresponding correlation for the furan and benzene series is a little poorer (correlation coefficient 0.983; intercept 0.04), with a slope of 1.04. It follows that there is a good correlation between the σ values for the furan and those for the thiophen systems

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[26] B. Bak, D. Christensen, W. B. Dixon, L. Hansen-Nygaard, J. Rastrup-Andersen, and M. Schottländer, *J. Mol. Spectroscopy*, 1962, **9**, 124; B. Bak, L. Hansen-Nygaard, and J. Rastrup-Andersen, *ibid.*, 1961, **7**, 58.

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(correlation coefficient 0.990; intercept 0.02; slope 1.00). The implication is that in so far as these calculations provide a valid guide, substituent effects should be (i) virtually identical for transmission through furan and thiophen, which is consistent with our experimental results, and (ii) only slightly greater for these than for transmission through benzene, which does not fit with our results. We cannot at present offer any explanation of the discrepancy in the latter case, but we should repeat that it cannot, in our view, be attributed to any effect of the departure from planarity in compounds (I) and (II). In order to match the ρ values given by variation of Y with X = H, the ρ values for variation of X with Y = H would have to be 4.0—4.6, and this would, in the light of general experience, be incompatible with the ρ values of *ca.* 2.7 observed for both acetophenones and fluorenones.

In spite of the general correlation noted above, there are some quite large differences between $\sigma_{5.2}$ constants for furan and σ_p constants for benzene in the case of the MeO ($\sigma_{5.2}$ −0.15; σ_p −0.27), Cl ($\sigma_{5.2}$ 0.34; σ_p 0.23), and NO_2 groups ($\sigma_{5.2}$ 0.91; σ_p 0.78). It is thus relevant to note that use of the σ_p constants for these groups in a correlation with log k_{rel} values for the $PhCOC_4H_2OY$-2 compounds gives a straight line through all three points and the origin (Y = H) (Figure 2), while use of the calculated $\sigma_{5.2}$ constants also gives a straight line through the three points but this misses the origin by 0.10 units. In other words, use of σ_p constants for the furan system gives better results than use of the $\sigma_{5.2}$ constants specially calculated for that system.

EXPERIMENTAL

Solvent.—Propan-2-ol was dried over calcium hydride, and freshly distilled from it before use.

Ketones.—(i) Previously known ketones, *viz.* compounds 2, 3, 8—10, 13—15, and 18 in Table 1 were made as previously described.[28]

(ii) Most new ketones (1, 4—6, 11, 12, 16, and 17) were made as follows. A solution of the appropriate acyl halide (0.045 mol) and thiophen, furan, or benzene (0.25 mol) in carbon disulphide (20 cm^3) was added with vigorous stirring to a suspension of anhydrous aluminium chloride (0.045 mol) in carbon disulphide (100 cm^3). Stirring was continued for 3 h, and the mixture was then added to crushed ice. Extraction with chloroform, washing of the extract with 10% aqueous sodium hydrogencarbonate, drying (Na_2SO_4), and evaporation of the extract gave a residue, which was chromatographed on silica with elution by benzene. Recrystallization was from n-hexane. In the preparation of 2-furyl *p*-nitrophenyl ketone, titanium tetrachloride was used in place of aluminium trichloride as catalyst.

(iii) Acetic anhydride (10 g) was added dropwise at −10 °C to nitric acid (*d* 1.50; 10.4 g) containing concentrated sulphuric acid (0.7 g). The mixture was kept at −20 °C while a solution of furyl phenyl ketone (5.2 g) in acetic anhydride (6.2 g) was added dropwise. The mixture was stirred for 1 h at −15 °C, then added to crushed ice. Work-up as under (ii) gave 2-*furyl* 5-*nitrophenyl ketone*.

(iv) A solution of 5-bromofuryl phenyl ketone (6.3 g, 0.025 mol) in anhydrous methanol (5 cm^3) was added dropwise to methanol (5 cm^3) in which sodium (1.7 g, 0.063 mol) had been dissolved. The mixture was refluxed for 1 h, then evaporated, and the residue was treated with 10% hydrochloric acid (100 cm^3), then extracted with ether. Removal of the ether from the extract left a residue which was chromatographed on silica with benzene as eluant to give 5-*methoxyphenyl* 2-*thienyl ketone*. Recrystallization was from n-hexane.

TABLE 5

Yields, m.p.s, and analyses for the new ketones (XC_6H_4CO)-5-Y-C_4H_2E

E	Y	X	Yield (%)	M.p. (°C)	Found (Required) (%) C	H	S
S	H	*p*-MeO	60	75	66.0 (66.0)	4.7 (4.6)	14.6 (14.7)
	H	*p*-Br	80	97	49.4 (49.4)	2.4 (2.6)	12.2 (12.0)
	H	*m*-Br	80	59	49.5 (49.5)	2.4 (2.6)	11.9 (12.0)
	H	*p*-NO_2	50	176—177	57.6 (56.6)	3.1 (3.0)	
	5-MeO	H	50	57	65.8 (66.0)	4.7 (4.6)	14.5 (14.7)
	5-NO_2	H	70	110	56.4 (56.6)	3.2 (3.0)	
O	H	*p*-MeO	60	63	71.3 (71.3)	5.0 (5.0)	
	H	*p*-NO_2	15	163—164	60.7 (60.8)	3.3 (3.2)	
	5-MeO	H	70	57	71.2 (71.3)	4.9 (5.0)	
	5-NO_2	H	45	120	60.8 (60.8)	3.4 (3.2)	

Yields, m.p.s, and analytical data for these new ketones are listed in Table 5.

Rate Measurements.—(i) A 0.0025—0.05M solution of sodium borohydride in propan-2-ol (20 cm^3) was mixed with a 0.003—0.06M solution of ketone in propan-2-ol (100 cm^3) at 25 °C. The mixture was kept at 25.0 ± 0.05 °C and samples (10 or 20 cm^3) were withdrawn at intervals and titrated against potassium iodate.[9] Reactions were followed to 80% completion, and rate constants were reproducible to within ±3%.

(ii) For phenyl 5-nitrofuryl or 5-nitrothienyl ketone the rate was too high for the above procedure, and the progress of the reaction was monitored by the change in the u.v. absorption at 300 nm of solution initially 9×10^{-5}M in sodium borohydride and 6×10^{-4}M in ketone. The cell holder was kept at 25.0 ± 0.1 °C.

I.r. Spectra.—Solutions in spectroscopic grade chloroform were examined in 1 mm cells with potassium bromide windows. Spectra were recorded in triplicate, and the frequencies calibrated against standards. Wavenumbers reported are thought to be accurate to within ±1 cm^{-1}.

We thank Dr. G. Seconi for valuable discussions.

[7/2165 *Received, 8th December,* 1977]

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