

Relative Reactivities and Activation Parameters for the Vilsmeier–Haack Formylation of Five-membered Heteroaromatic Compounds containing the Group VI Elements

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Rate constants and activation parameters are determined for the formylation by the $\text{HCONMe}_2\text{-COCl}_2$ complex in CHCl_3 , of furan, thiophen, selenophen, and tellurophen. ΔS^\ddagger Values are identical within experimental error, and the reaction is enthalpy controlled. The activation entropies are discussed in terms of the position of the transition states along the reaction co-ordinate, whereas ΔH^\ddagger values are correlated with 'empirical resonance energies' and ΔE_{log} . The results indicate that the transition states for all four compounds lie in a similar position along the reaction co-ordinate and that the differences in ground state energy play a fundamental role in determining the relative reactivities of the α -positions.

In the past few years the relative reactivities of five-membered heteroaromatic compounds towards electrophilic substitution at the α -position have been determined by the use of kinetic or competitive procedures. Re-

¹ P. Linda and G. Marino, *Chem. Comm.*, 1967, 499; *J. Chem. Soc. (B)*, 1968, 392.

² P. Linda and G. Marino, *J. Chem. Soc. (B)*, 1970, 43.

³ P. Linda and G. Marino, *Tetrahedron*, 1967, **23**, 1739.

actions allowing comparison of most rings include bromination by molecular bromine,^{1,2} tin tetrachloride-catalysed acetylation,^{3,4} trifluoroacetylation by trifluoroacetic anhydride,^{4,5} and Vilsmeier–Haack formylation.⁴

⁴ F. Fringuelli, G. Marino, G. Savelli, and A. Taticchi, *Chem. Comm.*, 1971, 1441.

⁵ S. Clementi, F. Genel, and G. Marino, *Chem. Comm.*, 1967, 498; S. Clementi and G. Marino, *Tetrahedron*, 1969, **25**, 4599.

The data accumulated show that, for the general case, the reactivity sequence is: pyrrole \gg furan $>$ tellurophen $>$ selenophen $>$ thiophen \gg benzene.⁶ However, no reasonable explanation of the reactivity order observed has been presented so far.

The current belief regards the reactivity as dependent on the high π electron densities of the rings.⁷ Thus, the greater reactivity of pyrrole than furan has been ascribed to the greater electronegativity of oxygen, and the greater reactivity of furan than thiophen has been taken as due to the greater conjugative, electron-donor power of the first row elements.⁷ Actually, the electron density at the carbon atoms is lower than in benzene; in fact a critical analysis of the dipole moments of these compounds indicates that in furan and thiophen,⁸ as well as in selenophen and tellurophen,⁹ the negative pole lies on the heteroatom.

Moreover, the fact that furan and thiophen are also more reactive than benzene towards nucleophilic substitution,¹⁰ in spite of the opposite electronic requirements of these reactions, suggests that electronic distribution is not the main factor in determining the overall reactivity scale.

The relative reactivities of monosubstituted benzenes towards electrophilic substitution depend on the relative stabilities of the intermediate carbon ions, but even this explanation is not sufficient to explain the relative reactivities of the heteroaromatic rings, since thiophen would be expected to react more rapidly than furan, because of the greater tendency of sulphur to bear a positive charge.

Another unsolved problem in electrophilic aromatic substitution is that of the position of the transition state along the reaction co-ordinate for the same substitution of various aromatic systems. The problem is of great topical interest. Some authors^{11,12} have expressed the opinion that the transition states of electrophilic aromatic substitutions are not rigidly fixed, always resembling the Wheland intermediate, but can lie, when the electrophilic species are sufficiently powerful, much earlier along the reaction co-ordinate, thus resembling the starting compounds. Since the same effect should be caused by a change in the substrate nucleophilicity, substitutions at five-membered rings can offer a suitable system to answer this question.

In previous papers on the trifluoroacetylation of substituted thiophenes, furans, and pyrroles¹³ we have tentatively attributed the different ρ values for the three rings to the different extent of formation of the new

σ bond and to a consequent difference in the positive charge developed in the transition state.

Some results are inconsistent with this reactivity-selectivity relationship, and the simultaneous application of the Hammett equation and the Hammond postulate¹⁴ has recently been criticised.¹⁵ An alternative explanation of the different sensitivities of furan and thiophen rings to substituent effects in the solvolysis of 1-aryl-ethyl *p*-nitrobenzoates has been suggested by Noyce and Forsyth.¹⁶ According to these authors an additional important factor in the variation of ρ with the nature of the aromatic substrate is the pattern of charge distribution within each ring, and, in particular, the amount of positive charge on the carbon atom bearing the substituent.

The problem under discussion (*i.e.* whether the transition state for the reactions of different rings has the same or a different position along the reaction co-ordinate) is also important from a theoretical point of view.

Many reactivity indices, based on different models for the transition states, have been determined for these molecules using MO calculations.⁶ Comparison between calculated reactivity indices for the different rings and the experimental data, is allowed, of course, only if the transition states have the same structure.

As a contribution to the resolution of these problems, it is useful to determine the activation parameters for a given electrophilic substitution. Among the reactions examined,¹⁻⁵ formylation with the dimethylformamide-carbonyl chloride complex in chloroform, has been chosen for the present work, because of the simple kinetics of the reaction.¹⁷

RESULTS AND DISCUSSION

The kinetic study was limited to the four five-membered rings containing the Group VI elements: furan, thiophen, selenophen, and tellurophen. In fact, under the experimental conditions the rate of substitution of pyrrole was too high and that of benzene too low to be followed by standard techniques.

All four substrates examined gave, under the conditions used, the expected 2-formyl derivatives. In all cases, linear second-order kinetic plots were obtained throughout the reaction range examined (up to 90%). Each compound was formylated at least at four different temperatures; the range was 20–50° for furan, thiophen, and selenophen and 20–35° for tellurophen, since at temperatures $>35^\circ$ it decomposes slightly under the reaction conditions.

The second-order rate constants and the activation parameters are reported in Table 1. All the Arrhenius plots were satisfactorily linear ($r > 0.994$). The errors

⁶ For a comprehensive review see G. Marino, *Adv. Heterocyclic Chem.*, 1971, **13**, 235.

⁷ J. H. Ridd, 'Physical Methods in Heterocyclic Chemistry,' Academic Press, New York and London, 1971, vol. 4, p. 95.

⁸ G. Marino, *J. Heterocyclic Chem.*, 1972, **9**, 817.

⁹ H. Lumbroso, M. C. Bertin, F. Fringuelli, and A. Taticchi, *J.C.S. Chem. Comm.*, 1973, 342.

¹⁰ D. Spinelli, C. Dell'Erba, and A. Salvemini, *Ann. Chim. (Italy)*, 1962, **52**, 1156; D. Spinelli, C. Dell'Erba, and G. Guanti, *Boll. sci. Fac. Chim. ind. Bologna*, 1967, **25**, 71.

¹¹ G. A. Olah, S. J. Kuhn, S. Flood, and J. C. Evans, *J. Amer. Chem. Soc.*, 1962, **84**, 3687; G. A. Olah, *Accounts Chem. Res.*, 1971, **4**, 240.

¹² E. Berliner, *Progr. Phys. Org. Chem.*, 1964, **2**, 253.

¹³ S. Clementi and G. Marino, *Chem. Comm.*, 1970, 1642; *J.C.S. Perkin II*, 1972, 71.

¹⁴ G. S. Hammond, *J. Amer. Chem. Soc.*, 1955, **77**, 334.

¹⁵ C. D. Johnson and K. Schofield, *J. Amer. Chem. Soc.*, 1973, **95**, 270; C. D. Johnson, *Chem. and Ind.*, 1973, 119.

¹⁶ D. A. Forsyth and D. S. Noyce, *Tetrahedron Letters*, 1972, 3893.

¹⁷ S. Alunni, P. Linda, G. Marino, S. Santini, and G. Savelli, *J.C.S. Perkin II*, 1972, 2070.

TABLE 1

Rate constants and activation parameters for formylation by the $\text{HCONMe}_2\text{-COCl}_2$ complex in chloroform

Substrate	$k_2/\text{mol}^{-1} \text{s}^{-1}$						Activation parameters	
	20.0°	25.0°	30.0° ^a	35.0°	40.0°	50.0°	$\Delta H^\ddagger/\text{kcal mol}^{-1}$	$\Delta S^\ddagger/\text{cal mol}^{-1} \text{K}^{-1}$
Furan	6.41×10^{-5}		1.19×10^{-4}		3.17×10^{-4}	7.01×10^{-4}	14.7 ± 1.1	-27.7 ± 1.8
Thiophen	3.60×10^{-7}	5.13×10^{-7}	1.11×10^{-6}	1.54×10^{-6}	2.53×10^{-6}	5.73×10^{-6}	17.1 ± 0.8	-29.5 ± 1.1
Selenophen	1.79×10^{-6}	2.65×10^{-6}	4.04×10^{-6}		1.00×10^{-5}	2.71×10^{-5}	16.5 ± 0.7	-28.8 ± 1.0
Tellurophen	1.61×10^{-5}	2.62×10^{-5}	4.08×10^{-5}	5.93×10^{-5}			15.5 ± 1.2	-27.5 ± 2.1

^a The values at 30° are slightly different from those in ref. 4 (see text).

in the figures for ΔH^\ddagger and ΔS^\ddagger was evaluated from the appropriate estimated standard errors of the regression coefficients giving average values of $0.9 \text{ kcal mol}^{-1}$ for $\Delta\Delta H^\ddagger$ and $1.5 \text{ cal mol}^{-1} \text{K}^{-1}$ for $\Delta\Delta S^\ddagger$.

The data in Table 1 show that the activation entropies are constant (within error) for all four members of the series. This fact may indicate that the disposition of the atoms around the reaction centre is similar, or, in other words, that the transition states of all four rings lie in a similar position along the reaction co-ordinate. Moreover the high negative ΔS^\ddagger values (*ca.* $-28 \text{ cal mol}^{-1} \text{K}^{-1}$) are consistent with a high degree of formation of a new bond, *i.e.* the transition states resemble σ complexes.¹⁸

Therefore, the relative rates of formylation are controlled by the activation enthalpies. The figures are compared in Table 2 with the corresponding data for SnCl_4 -catalysed acetylation by acetic anhydride and for the reaction with trifluoroacetic anhydride in dichloroethane.

TABLE 2

Relative reactivities of five-membered heterocyclic compounds containing the Group VI elements in electrophilic substitutions

Substrate	k/k_{Th}^a		
	$\text{Ac}_2\text{O-SnCl}_4$ at 25°	$(\text{CF}_3\text{CO})_2\text{O}$ at 75°	$\text{COCl}_2\text{-HCONMe}_2$ at 30°
Furan	11.9 ^b	140 ^c	107 ^d
Thiophen	1	1	1
Selenophen	2.28 ^{e,f}	7.33 ^{e,f}	3.64 ^d
Tellurophen	7.55 ^e	46.4 ^e	36.8 ^d

^a Reactivities relative to thiophen. ^b Ref. 3. ^c Ref. 5.^d Calculated from data in Table 1. ^e Ref. 4. ^f Data for selenophen are slightly different from those in ref. 2 as further runs were carried out.

Whereas the relative reactivities of different mono-substituted derivatives of benzene towards electrophilic substitution are mainly related to the relative stabilities of the corresponding intermediate carbonium ions, apparently the sequence of reactivities of the five-membered heterocyclic compounds is more dependent on the relative energies of the molecules in their 'ground states'. Qualitatively, it is observed that the more aromatic the starting molecule, the smaller is the rate of substitution. The order of reactivity is, in fact, the reverse of the order of the ground-state aromaticities, as measured by several different techniques:¹⁹ thiophen > selenophen > tellurophen > furan.

Quantitatively, a linear correlation ($r 0.994$) is obtained when the activation enthalpies for the formylation are

* For furan (23 kcal mol^{-1}) and thiophen (31 kcal mol^{-1}) the resonance energies reported by Pauling²⁰ were used. For selenophen (29 kcal mol^{-1}) and tellurophen (25 kcal mol^{-1}) the values estimated in ref. 19 were used.

plotted against the resonance energies of the four rings* (Figure 1). This indicates that the differences in ground state energy play a fundamental role in determining the relative reactivities of the α positions.

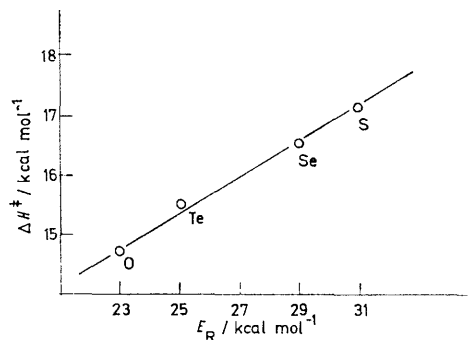
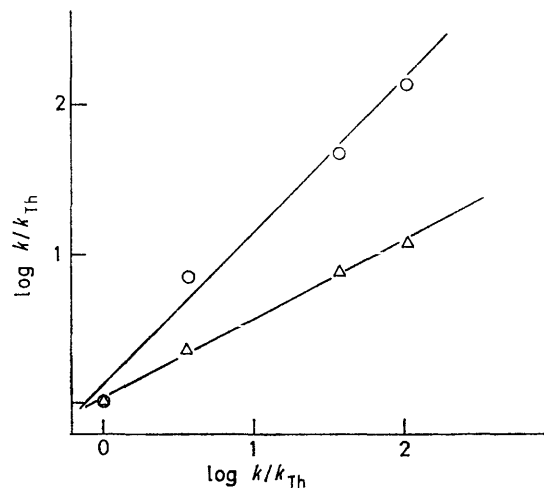


FIGURE 1 Plot of activation enthalpies for formylation of furan (O), thiophen (S), selenophen (Se), and tellurophen (Te) against their resonance energies

FIGURE 2 Relative reactivities ($\log k/k_{\text{thiophen}}$) for acetylation (Δ) and trifluoroacetylation (O), against the relative reactivities for formylation

The above conclusions are probably not limited to the formylation alone, but can possibly be extended to other electrophilic substitutions of these rings, as suggested by the fact that good linear correlations are obtained when the $\log k/k_{\text{Th}}$ values for acetylation or trifluoroacetylation are plotted against the $\log k/k_{\text{Th}}$ values for formylation (Figure 2).

¹⁸ R. Taylor 'Kinetic of the Electrophilic Aromatic Substitution,' eds. C. M. Banford and C. F. H. Tipper, 'Reaction of Aromatic Compounds,' Elsevier, Amsterdam, 1972, p. 174.

¹⁹ F. Fringuelli, G. Marino, A. Taticchi, and G. Grandolini, *J.C.S. Perkin II*, in the press.

²⁰ L. Pauling, 'The Nature of the Chemical Bond,' Cornell Univ. Press, Ithaca, 3rd edn., 1945.

Comparison with Theoretical Reactivity Indices.—The electron densities, implying a transition state similar to the initial state, and localization energies, implying a transition state similar to the Wheland intermediate, are the most common theoretical quantities taken as reactivity indices.

Recent CNDO/2 calculations on the electronic structures of the four congeners²¹ as well as many other data on heterocyclic compounds available in the literature,⁶ and discussed in the Introduction, show that electron density is not a good reactivity index for explaining the relative reactivities in electrophilic substitution.

Moreover, in view of the highly negative ΔS^\ddagger values, the localization energies (ΔE_{loc}), defined as the difference in energy between the aromatic compound and the appropriate Wheland intermediate, appear to be a more useful theoretical reactivity index for a series of related substrates towards the same electrophilic substitution. For this case, in fact, linear correlations between the rate constants (or ΔH^\ddagger values) and the localization energies are predicted by Dewar²² according to equations (1) and (2) where A , B , C , and D are reaction constants, with the assumptions that for all substrates (a) the structures of the transition states are close to those of the Wheland intermediates, (b) the transition states lie at the same position along the reaction co-ordinate, (c) the activation entropies are very similar, and (d) the total energy variations due to solvation, to the formation of the new CX bond (where X is the electrophile), and to the change in hybridization of the carbon atom at which the substitution takes place, are constant.

$$\log k = A + B \Delta E_{loc} \quad (1)$$

$$\Delta H^\ddagger = C + D \Delta E_{loc} \quad (2)$$

The localization energies have recently been calculated by Galasso²¹ for electrophilic substitutions of furan, thiophen, selenophen, and tellurophen, by the CNDO/2 method using the α -protonated molecule as a model for the transition state. The reported values, in atomic units, for α -substitution are furan 0.6193, thiophen 0.5813, selenophen 0.5737, and tellurophen 0.5382, a smaller figure denoting a more reactive system. The value for furan is clearly not reliable, being at variance with all the experimental data available.⁶ Since Galasso's calculations predict even higher reactivity of the β -relative to the α -position for furan this probably is due to imperfect parametrisation for oxygen.*

Good agreement between experimental and theoretical predictions [equations (1) and (2)] is found for the other three rings. In fact linear correlations are obtained when the localization energies are plotted against both the experimental ΔH^\ddagger and $\log k$ values for the formylation.

* It must be noted that previous SCF calculation by Hermann,²³ give the correct site of electrophilic attack at the furan ring. This reinforces the opinion that the values for the localization energies reported by Galasso²¹ are not reliable.

²¹ V. Galasso, personal communication.

²² M. J. S. Dewar, 'Molecular Orbital Theory of Organic Chemistry,' McGraw-Hill, New York, 1968, ch. VIII.

EXPERIMENTAL

Materials.—Furan, b.p. 32°, and thiophen, b.p. 83–84°, were pure commercial samples, purified by distillation at atmospheric pressure. Selenophen,²⁴ b.p. 110°, and tellurophen,²⁵ b.p. 92° at 100 mmHg, were prepared as previously described.

A number of products was required as standards for g.l.c. analysis: furan-2-carbaldehyde, thiophen-2-carbaldehyde, and acetophenone were commercial samples. Tellurophen-2-carbaldehyde,²⁴ 2-acetylfuran,³ 2-acetylthiophen,³ 2-acetylselenophen,² 2-acetyltellurophen,²⁴ 2-trifluoroacetylfuran,⁵ 2-trifluoroacetylthiophen,⁵ and 2-trifluoroacetylselenophen² were available from previous studies.

2-Trifluoroacetyltellurophen was prepared by heating a mixture of tellurophen (2.1 g) and trifluoroacetic anhydride (1.95 ml) in 1,2-dichloroethane (15 ml) in a sealed tube at 75° for 56 h. After the usual work-up, the residue was chromatographed on silica gel (Merck PF 254), elution with light petroleum (b.p. 40–70°) giving 2-trifluoroacetyltellurophen (1 g), b.p. 85° at 15 mmHg, ν_{CO} (film) 1680 cm^{-1} , τ (100 MHz; CCl_4) 1.94 (1H, q, $J_{4,5}$ 6.6, $J_{4,3}$ 4.5 Hz, 4-H), 1.35 (1H, m, 3-H), and 0.40 (1H, q, $J_{4,5}$ 6.8, $J_{3,5}$ 1.4 Hz, 5-H).

1,2-Dichloroethane, acetic anhydride, trifluoroacetic anhydride, dimethylformamide, and chloroform were purified by standard procedures. Commercial tin tetrachloride and carbonyl chloride were used without further purification.

Competitive Acylations.—These were carried out as described previously^{3,5} and the results are in Table 2. The values for selenophen are slightly different from those in ref. 2 because more runs were carried out. Data for tellurophen obtained by the direct ratio $k_{Te} : k_{Th}$ were confirmed by the product $k_{Te} : k_{Se} \times k_{Se} : k_{Th}$.

Kinetics of Formylation.—The preparation of the dimethylformamide-carbonyl chloride complex and the kinetic procedure were described previously.¹⁷ The mean k values at each temperature are in Table 1.

Activation Parameters.—Activation enthalpies and entropies were calculated by applying a least square analysis to equation (3).

$$\log (k/T) = 10.319 + \Delta S^\ddagger/4.574 - \Delta H^\ddagger/4.574T \quad (3)$$

The magnitude of the errors in ΔH^\ddagger and ΔS^\ddagger reported in Table 1 was evaluated by the appropriate relationships (4) and (5) involving the standard error of the regression coefficient (s_b) and the prediction interval for the intercept (s_a).²⁶

The estimates s_b and s_a are given by equations (6) and (7) respectively where $s_{y/x}$ is the standard error of estimate, \bar{x} the mean value of the independent variable, and s_x its standard deviation.

$$b \pm s_b \quad (4)$$

$$a \pm s_a \quad (5)$$

$$s_b = s_{y/x} [s_x(n-1)^{\frac{1}{2}}] \quad (6)$$

$$s_a = s_{y/x} \left[1 + \frac{1}{n} \frac{\bar{x}^2}{(n-1)s_x^2} \right]^{\frac{1}{2}} \quad (7)$$

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²³ R. B. Hermann, *Internat. J. Quantum Chem.*, 1968, **2**, 165.

²⁴ L. Chierici and G. Pappalardo, *Gazzetta*, 1958, **88**, 453.

²⁵ F. Fringuelli and A. Taticchi, *J.C.S. Perkin I*, 1972, 199; *Ann. Chim. (Italy)*, 1972, **62**, 777.

²⁶ E. L. Crow, F. A. Davis, and M. W. Maxfield, 'Statistical Manual,' Dover, New York, 1960.