THIOPHENE AND ITS DERIVATIVES

Part Two

Edited by

Salo Gronowitz

University of Lund
Lund, Sweden

AN INTERSCIENCE® PUBLICATION
JOHN WILEY AND SONS
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Part Two

This is the Forty-Fourth Volume in the Series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER and EDWARD C. TAYLOR

Editors

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The Chemistry of Heterocyclic Compounds

The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. It is equally interesting for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocyclic compounds.

A field of such importance and intrinsic difficulty should be made as readily accessible as possible, and the lack of a modern detailed and comprehensive presentation of heterocyclic chemistry is therefore keenly felt. It is the intention of the present series to fill this gap by expert presentations of the various branches of heterocyclic chemistry. The subdivisions have been designed to cover the field in its entirety by monographs which reflect the importance and the interrelations of the various compounds, and accommodate the specific interests of the authors.

In order to continue to make heterocyclic chemistry as readily accessible as possible, new editions are planned for those areas where the respective volumes in the first edition have become obsolete by overwhelming progress. If, however, the changes are not too great so that the first editions can be brought up-to-date by supplementary volumes, supplements to the respective volumes will be published in the first edition.

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Preface

In 1952, in the first volume of *The Chemistry of Heterocyclic Compounds*, Howard D. Hartough described the state of research on the chemistry of thiophene and its derivatives up to 1950. Selenophene and tellurophene were also included in this monograph which, except for two chapters was written by Hartough alone. When this book was written, the explosive development triggered by the commercial process for thiophene from butane and sulfur, developed by Socony-Vacuum Oil Company in the 1940's, had just begun. The enormous amount of work carried out on this important aromatic five-membered heterocycle since 1950 makes it of course impossible for one person to cover all aspects, and an able group of specialists were assembled from all over the world to treat the entire field. This makes some minor overlaps between chapters unavoidable, but I think it is important to treat some topics from different angles of approach.

Because of the wealth of results and the rather large number of contributors, these volumes are not as strictly organized as some previous volumes in this series, but can be considered as a collection of topics on thiophene chemistry. Together, however, it is my hope that these chapters give as comprehensive a description as possible of the chemistry of thiophene and its monocyclic derivatives, based on the literature from 1950 to 1982. References to previous results, treated in Hartough's book, are also given when necessary.

The chapters fall in two categories: (1) those that treat syntheses, properties, and reactions of thiophenes, and (2) those that treat systematically functionalized simple thiophenes, such as alkylthiophenes, halothiophenes, aminothiophenes, thiophenecarboxylic acids, and so on. The latter chapters, as is customary in the Weissberger–Taylor series, contain tables of compounds with their physical properties, which should be very useful for all synthetic chemists. Part 1 of these volumes contains only chapters in category (1) and starts with a treatise on the preparation of thiophenes by ring-closure reactions and from other ring systems. It is followed by a chapter on theoretical calculations. Then, in two chapters, naturally occurring thiophenes in plants and in petroleum, shale oil, and coals are treated. The topic of the next chapter is the important field of pharmacologically active compounds. The synthetic use of thiophene derivatives for the synthesis of aliphatic compounds by desulfurization follows. Two chapters treat thiophenes modified at the sulfur, namely thiophene-1,1-dioxides and thiophene-1-oxides, and *S*-alkylation of thiophenes. In the last three chapters, the discussion on different reactivities of thiophenes starts with radical reactions of thiophenes, cycloaddition reactions, and photochemical reactions.

Part 2 of this four-part volume begins with a treatment of the important field of electrophilic aromatic substitution of thiophenes, followed by systematic treatment of four classes of functionalized thiophenes, namely the alkyl-, halo-, nitro- and aminothiophenes.

The first two chapters of Part 3 of this volume treats the chemistry of thiophene derivatives containing thiophene-to-oxygen bonds and thiophene-to-sulfur bonds, respectively, and the remaining chapters cover formyl and acyl derivatives of thiophene, thiophenecarboxylic acids, and thenyl derivatives.

In Part 4, nucleophilic aromatic substitution of thiophenes, physical properties of thiophenes, metal derivatives of thiophenes as well as thienyl ethenes, thienyl acetylenes, and aryl- and hetero-arylthiophenes will be examined.

I wish to thank all the distinguished scientists who contributed chapters to these volumes for their splendid cooperation and my secretary Ann Nordlund for her invaluable help. I am also indebted to Dr. Robert E. Carter for correcting my chapter and those of some of the other authors whose native tongue is not English.

SALO GRONOWITZ

Lund, Sweden
January 1986

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This is the Forty-Fourth Volume in the Series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

CHAPTER I

Electrophilic Substitution of Thiophene and Its Derivatives

ROGER TAYLOR

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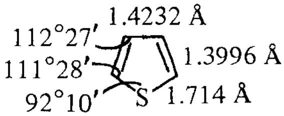
I. INTRODUCTION

1. Aromaticity and Reactivity

Electrophilic substitution in thiophene (which has been reviewed previously[1-3]) occurs more readily than in benzene and takes place preferentially at the α position; it is the least reactive of the five-membered heterocyclic aromatics which contain one heteroatom. To understand the reason for this and also for the directing effects of substituents, it is first necessary to consider some basic facts about the molecule.

Like all the five-membered heterocycles, thiophene is classed as electron-rich, there being six π electrons delocalized over five atoms. The occurrence of delocalization is confirmed by the structure of the molecule (elucidated from the microwave spectrum)[4] given in **1**. This shows that the C–S, C–C, and C=C bonds are respectively shorter, longer, and shorter than they would be in an isolated state, when values of ca. 1.82, 1.54, and 1.38 Å would apply. Given that delocalization occurs, then the ring must have a higher π density than in benzene, and the greater ease of electrophilic substitution follows.



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Prediction of the reactivity relative to other five-membered heterocycles is less easy. A priori it might seem that the less aromatic the heterocycle, the less stable it will be and the greater the ease of electrophilic substitution, but this turns out to be only approximately true. There are three principal measures available for assessing the aromaticity of these compounds:

1. Resonance energies,[5,6] which give the aromaticity order: benzene ≫ thiophene ⩾ pyrrole > selenophene > tellurophene > furan.
2. NMR ring currents[7], which predict the order: thiophene > pyrrole > furan (although this conclusion is disputed[8]).
3. The bond length ratios C_2-C_3/C_3-C_4 (one cannot use the $X-C_2$ bond lengths because these are very dependent upon the size of the heteroatom X). They also predict the order: (benzene) > thiophene > pyrrole > selenophene > furan.[4,9]

In addition, bond-electron gradients give the order: thiophene ~ pyrrole > furan, while molar magnetic rotations and magnetic moment susceptibilities both give the order: thiophene > pyrrole > furan.[10]

Thus although all the five-membered heterocycles are correctly predicted to be much more reactive than benzene, the reactivity order within the heterocyclic series is wrong. This is because an important factor is the polarizability of the molecule, that is, the ability of the heteroatom to release electrons under conditions of high electron demand (the +E effect in Ingold's notation) such as will apply in the transition state of the reaction with electrophiles. This polarizability is well established to be greater the less electronegative the atom, so that the order of polarizability for substituents in benzene is NR_2 > OR. The effect of this is to make pyrrole much more reactive than furan.

Within Group VIA the evidence (judged by the difference between σ_p^+ and σ_p values[11]) is that sulfur is more polarizable than oxygen, so that the difference in electronegativities is more important than the difference in the size of the carbon and heteroatom *p* orbitals. This being so, we would expect the overall polarizability sequence to be Te > Se > S > O, that is the minimum occurs with oxygen. (In Group VIIA the different balance of electronegativities and orbital size is such that

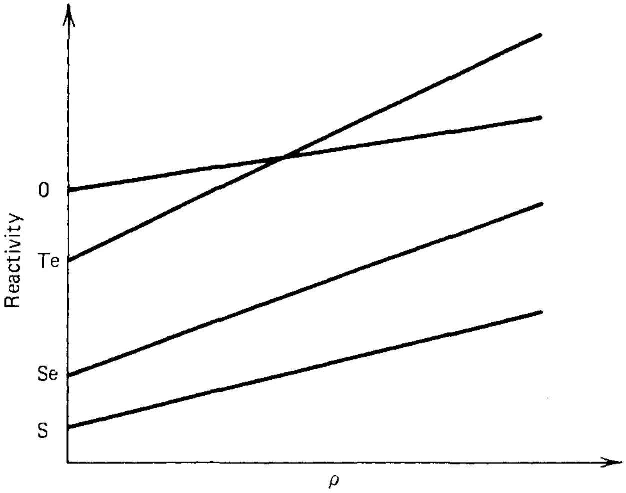


Figure 1

the minimum, again deduced from the difference[12] in $\sigma_p{}^+$ and σ_p, occurs with bromine.) If the polarizability of the Group VIA elements is superimposed upon the ground-state order of aromaticity, then we can have a result as illustrated in Fig. 1, where the vertical axis represents reactivity and the horizontal axis represents increasing electron demand in the transition state; the slopes of the lines are therefore proportional to the polarizabilities of the heteroatoms. Obviously we shall be able to obtain either of the reactivity orders O > Te > Se > S and Te > O > Se > S, and indeed both have been observed. As is the case with substituents on benzene, although we may assign a σ^+ value that will approximately describe the quantitative electrophilic reactivity of the aromatic (or in this case the heterocycle), it is clear that the polarizability effect will make these σ^+ values unsatisfactory for accurately predicting the reactivity in all reactions, although they will give a reasonable overall picture of that reactivity. This is considered further in Section II.

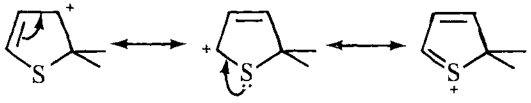
2. Theoretical Calculations of Reactivity

There are two methods for calculating the reactivity of thiophene: the valence bond method and the molecular orbital method.

A. The Valence Bond Method

Although very simple and only semiquantitative, the valence bond method is able to predict correctly the most reactive site, which is not the case for some of the molecular orbital (MO) methods described below.

For substitution at the 2 and 3 positions, the approximate canonicals representing the transition state are 2 and 3, respectively. Since there are more structures in the former case, the 2 position will be more reactive than the 3 position. However, we cannot tell if either will be more or less reactive than a position in benzene, because we cannot weigh structures with heteroatoms against those without. For this we must in principle turn to molecular orbital (MO) calculations.



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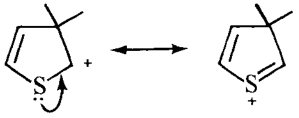

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B. The Molecular Orbital Method

The molecular orbital (MO) method gives two measures of reactivity: π-electron density and the localization energy. These are relevant to reactions having transition states very close to the ground state or to the Wheland intermediate (as does the valence bond method), respectively. However, for most reactions, the transition states are well between these extremes. Moreover, the π densities relate to a situation where the polarizability of sulfur is not involved, so that the $-I$ effect of sulfur dominates, whereas localization energies relate to the situation where polarizability is at a maximum. Thus there are two opposing effects, so unless the structure of the transition state is precisely known *and* can be included in the calculations, the results are likely to be, and indeed are, poor. Calculations also have the following additional problems: (1) Which parameters should be used for the Coulomb and resonance integrals, etc? (2) Should the *d* orbitals of sulfur be taken into account? (3) Which calculations are the most appropriate?

With regard to the latter, there have been Hückel, SCF (including CNDO/2), and ab initio (STO 3G) calculations.[13–35] In the Hückel calculations, values for the Coulomb integral (a measure of the electronegativity of the heteroatom) and the resonance integral (a measure of the degree of overlap between two adjacent atoms) have to be selected. The Coulomb integral for sulfur α_S is usually chosen to be the same as that for carbon α_C, and a value between 0.5 and 0.7 is commonly used for the resonance integral β_{CS} (cf. $\beta_{CC} = 1.0$). In some calculations (e.g., Ref. 20), the low bond order of the $C_3{-}C_4$ bond has been taken into account, with $\beta_{3,4} = 0.642$; too large a value of α_S results in the predicted reactivity of the 2 position being too low. The effect of including the 3*d* (and also the 4*s* and 4*p*) electrons is greater on the σ than on the π density,[25,26] and seems to predict too low a reactivity for the 3 position relative to benzene. The results of π-density calculations are given in Table 1, from which it can be seen that the method leaves much to be desired, but the majority of calculations predict the correct result. Localization energies predict the

TABLE 1. MOLECULAR ORBITAL PREDICTIONS OF POSITIONAL REACTIVITY ORDER IN THIOPHENE

Order	References
(a) π-Charge Densities	
3 > 2 > benzene	17,20,22
3 = 2 = benzene	13,15
2 > 3 > benzene	14,18,19,21,23,24,27,31,34,35
2 > benzene > 3	16,23,28,32
(b) Localization Energies	
2 > 3 > (benzene)	19,20,25,30,33

correct order in each case. The order 2-Se > 2-S > 3-Se > 3-S is also predicted by these calculations,[32,33] but the predicted reactivity order for furan is completely wrong. In the writer's experience it appears to be the case that the further a molecule is, in both the number of heteroatoms and electronegativity of the heteroatom, from a purely carbocyclic system, the less reliable the calculations.

The parameters $\alpha_S = \alpha_C$ and $\beta_{CS} = 0.6\,\beta_{CC}$ predict the correct order not only in thiophene but also in the sulfur-containing ring of benzo[*b*]thiophene and thienothiophenes (allowing for the fact that the α positions are effectively equal in reactivity[36,37]). The correct order is also predicted in each of the three dithienobenzenes and in each of the three dithienothiophenes.[38,39] Indeed if all 8 positions of the former group are taken together, and all 12 positions in the latter group, there are only trivial discrepancies in the overall orders. These parameters would seem to be optimal for the Hückel method. CNDO/2 calculations also give good results for the dithienobenzenes[30] and would probably do so for the thienothiophenes.

II. THE QUANTITATIVE ELECTROPHILIC REACTIVITY OF THIOPHENE

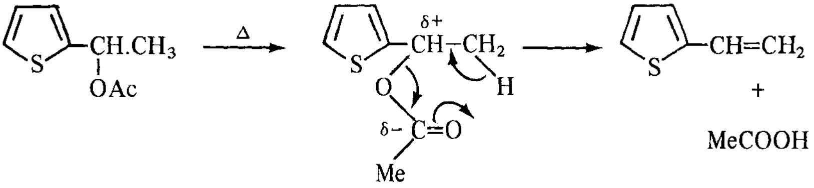
The electrophilic reactivity of thiophene has been determined in one of two ways, either directly by electrophilic substitution or by indirect methods using reactions in the side chain of thiophene derivatives.

1. Direct Electrophilic Substitution

Two methods are used here. The first is to react thiophene with the electrophile, measure the amount of α- and β-substitution, and determine the extent of substitution relative to that in benzene under the same conditions. From these data the partial rate factors, that is, the rates of substitution at a given site relative to that of a single site in benzene, can be determined. This method is used, for example, in halogenation and acylation. The second method involves "prelabeling" the sites in benzene and thiophene, for example, with tritium or a trimethylsilyl group, and the relative rates of removal of the label give the partial rate factor directly. This method is used in protiodetritiation, protiodesilylation, and so on.

2. Generation of Carbocations at the Side Chain

In these methods, a carbocation is generated at the side-chain α position, and the extent to which this cation is stabilized by thiophene relative to benzene is determined through rate measurements. This method, introduced by H. C. Brown for determining σ^+ constants,[40] was first applied by the writer to the determination of heterocyclic reactivities in 1962,[41] using the pyrolysis of 1-arylethyl acetates, a reaction that has the great advantage of the absence of solvent. Thus for measuring the reactivity of the α position of thiophene, the rate of the reaction as in **4** would be followed.



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By these two general methods the σ^+ values for the α and β positions of thiophene have been determined, and these are given along with those for furan in Table 2. Some reactions evidently give extreme or anomalous values, and possible reasons for this are described below. Even with these values disregarded, caution is needed in interpreting the remaining results. The values show that, as in the case of substituted benzenes, such as anisole, the σ^+ values are not reaction-independent and tend to be smaller in reactions of low ρ factor where there is less demand for resonance; this is particularly noticeable for the β position. Consequently it is unacceptable to average the σ^+ values (as others have done*),[55] particularly since if the same is done for furan, for which the σ^+ values have not been measured in high ρ-factor reactions (these are the ones in which furan decomposes), the *average* σ^+ value for the β position of furan turns out to be *less* than that for the β position of thiophene. It has therefore been claimed (and this is all too frequently quoted in papers as fact) that the β position of thiophene is more reactive than the β position of furan.[55] Yet except in acetylation (where a side reaction is almost certainly

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*One method for doing this that is mathematically unsatisfactory, since it obscures real deviations, is to plot log k_{rel} against ρ and draw a straight line through the spread of points; the slope of this line is said to be the σ^+ value and will generally differ from the average value determined statistically. (The misleading nature of these plots also delayed for many years the realization that the σ^+ values for the *m*-alkyl substituents, determined from solvolysis of *tert*-cumyl chlorides,[40] are substantially in error due to the effects of steric hindrance to solvation.[56])

TABLE 2. LOGARITHMS OF PARTIAL RATE FACTORS, AND σ^+ VALUES FOR ELECTROPHILIC SUBSTITUTIONS AND RELATED REACTIONS OF THIOPHENE AND FURAN

		Thiophene				Furan				
Reactions	ρ	$\log f_2$	σ_2^+	$\log f_3$	σ_3^+	$\log f_2$	σ_2^+	$\log f_3$	σ_3^+	References
A. Electrophilic substitutions										
1. Protiodemercuriation	–2.87	3.23	(–1.125)			3.60	(–1.25)	2.176	(–0.76)	42
2. Protiodesilylation	–4.6	3.61	–0.785	1.987	–0.43	4.17	–0.905	2.068	–0.45	43
3. Mercuriation	–4.0	6.26	(–1.565)							44,45
4. Iododeboronation	–4.76	4.0	–0.84	2.845	–0.60					46
5. Protiodeboronation	ca. –5.0	5.93	–1.16	3.85	–0.76	5.96	–1.19	3.85	–0.77	47,47a
6. Positive bromination	–6.2	5.30	–0.85	3.20	–0.52					45
7. Protiodetritiation	–8.75	7.99	–0.94	4.90	–0.56					37,48
8. Acetylation	–9.1	6.43	–0.71	4.13	–0.45	7.51	–0.825	3.67	–0.40	45
9. Molecular chlorination	–10.0	7.59	–0.76	5.59	–0.56	9.28	–0.93			45,49
10. Molecular bromination	–12.1	9.71	–0.80	7.02	–0.58	11.79	–0.97			45,49
B. Reactions producing side-chain cations										
11. Pyrolysis of 1-arylethyl acetates	–0.66	0.52	–0.795	0.255	–0.38	0.585	–0.885	0.273	–0.415	34
12. Rearrangement of arylpropenyl carbinols	–2.6	1.54	–0.595			1.954	–0.75			50
13. Isomerization of *cis*-1-aryl-2-phenylethenes	–3.3	2.544	–0.77							51
14. Solvolysis of 1-arylethyl chlorides	–5.4	4.206	–0.78							52
15. Solvolysis of 1-arylethyl acetates	–5.7	4.732	–0.83	2.681	–0.47	5.32	–0.93	2.83	–0.50	53
16. Solvolysis of 1-arylethyl *p*-nitrobenzoates	–6.0	4.80	–0.80	3.00	–0.50	5.0	–0.87			51

Values of σ^+ have also been reported (without any rate data) for the reaction of arylsulfonyl chlorides with aniline. Since this reaction has a *positive* rho factor and the transition state was said to be *negatively* charged (Ref. 54) the determination of electrophilic substituent constants from this reaction would seem to be invalid.

involved) *this is untrue for any reaction in which the reactivities of both positions have been compared under identical conditions.*

Some qualification of the data in Table 2 is necessary. For mercuriation the extremely high reactivity of the α position coupled with the total lack of any β product suggests that a coordination mechanism not available in benzene and with a lower activation energy is involved. It could be argued that the same ought therefore to be true of protiodemercuriation, which also gives anomalously high reactivities for both positions. However, although this is expected by the principle of microscopic reversibility, against this must be set the fact that while exalted values are obtained for both furan and thiophene in protiodemercuriation, the difference in the σ^+ values for the 2 positions is the same as in the other reactions; it is highly unlikely that both furan and thiophene would coordinate to mercury to the same extent. A coordination mechanism favoring the 2-substitution of furan also seems to be ruled out by the difference between the σ^+ values for the 2 and 3 positions being the same as for the other reactions. The implication is that the ρ factor for protiodemercuriation does not apply to these reactive substrates, that is, a different mechanism applies. Indeed, the correlation of the rate data for the substituted benzenes with σ^+ constants showed clear curvature. A comprehensive reexamination of both mercuriation and protiodemercuriation would probably be very valuable.

Similar doubts attend the data for protiodeboronation, because although this reaction gives exalted values for both the 2 and 3 positions of thiophene, the *difference* between them is again the same as in the other reactions, indicating that a higher ρ factor ought to apply, and it is probably relevant that protiodeboronation, like protiodemercuriation, is a reaction with marked kinetic complexities.[57]

Of the other reactions, the σ^+ values for protiodetritiation are higher than given previously,[52] and are corrected for hydrogen bonding, now known to reduce the reactivity of thiophene[37] (and much more so for furan). This may affect the data for any other reaction in which strong acids are used or are produced during the reaction. Either this or coordination of the heteroatom with the Lewis acid catalyst (which is so strong with pyrrole that it will not react at all in the presence of such catalysts)[58] is the probable cause of the depressed values in acetylation. This is further indicated by the fact that the difference in the reactivity of furan and thiophene is less than in other reactions (furan would coordinate or hydrogen-bond most), and the 3 position of furan is anomalously less reactive than the 3 position of thiophene.

Taking the data overall, the positional reactivity order is clearly 3-thiophene < 3-furan ≪ 2-thiophene < 2-furan, the increments in the σ^+ values relative to that for the former position being $-0.03, -0.36, -0.46$.

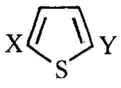
A few rate data have been obtained for selenophene and tellurophene. At the 2 positions, the order in formylation, acetylation, and trifluoroacetylation is furan > tellurophene > selenophene > thiophene,[59] and this parallels somewhat the reactivity order of the halogen substituents, where the higher polarizability and weaker inductive effect of the elements of higher atomic number can produce a higher overall electron release under conditions of high electron demand than for elements of lower atomic number. In solvolysis of 1-arylethyl acetates, however, the order becomes tellurophene > furan > selenophene > thiophene, with σ^+ values for the 2 positions of selenophene and tellurophene being −0.884 and −0.996, respectively;[60] in pyrolysis of 1-arylethyl acetates, the value for the former position was determined as −0.855, but side reactions prevented any value being obtained for the 2 position of tellurophene.[61] Whether the difference in the reactivity orders in solvolysis and acylation is due to higher demands for resonance in the former reaction or to interaction of tellurium with the acylating reagents is not clear at this time, although it may be significant that tellurophene was rather unstable under the acylation conditions.[59]

III. EFFECTS OF SUBSTITUENTS IN THIOPHENE

1. The Ability of Thiophene to Transmit Substituent Effects

Proper understanding of this aspect is important in the context of electrophilic substitution of thiophene, because it governs the extent to which further substitution will or will not occur after entry of the first electrophile. The relevance of the application of the Hammett equation to heteroaromatic compounds in general has attracted considerable interest, the subject being first reviewed in 1964 by Jaffé and Jones.[62]

Most work on five-membered heterocycles has been carried out with thiophene. Investigations have centered on whether substituent effects of X upon reaction at Y can be correlated with σ_p values in **5** and with σ_m values in **6** and **7**. (In the case of electrophilic substitutions and related reactions, the corresponding σ^+ values are used.) Correlations are indeed obtained[63–74] (though not always very good ones), and the ρ factors are generally different from those obtained from the corresponding reactions of the substituted benzenes. This difference has often been described in terms of the difference in the ability of −S− vs. −CH=CH− to transmit electronic effects (e.g., Ref. 75) but this is rather misleading. The relative values for the ρ factors for reactions of thiophenes and benzenes vary in a seemingly unsystematic way, showing that a number of factors are involved. These have not previously been rationalized, and a brief but full account is given here.



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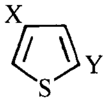

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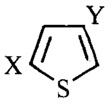

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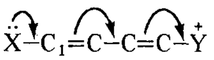
The ρ factors are a measure of three effects:

1. The ability of a substituent to act in the same way in different environments. It has been generally assumed that this ability will be constant. However, it is clear

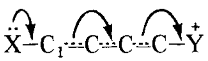
(see below) that steric effects are less in thiophene than in benzene because of the greater distance between adjacent hydrogens or between hydrogen and the sulfur orbitals. Consequently, the nitro, acetyl, carboxy, and carboalkoxy groups (and probably even methoxy groups) are able to become more coplanar with the thiophene ring than with the benzene ring, and this undoubtedly alters their electronic effects. Part of the discrepancies in the reactions described below probably derive from this effect, and it is recommended that the reader examine carefully any set of data before drawing any detailed conclusions. In particular, Hammett correlations that do not pass through the point for the unsubstituted heterocycle require very cautious interpretation.

2. The amount of charge developed in the transition state of a particular reaction. There are clearly two different classes of reactions here: those in which the aromatic is attached to a side chain in which a charge is developed and those (electrophilic substitutions) in which the transition state is developed as the electrophile approaches the ring. It is generally assumed that the transition state structure can vary according to the reactivity of the aromatic and thus, for example, the transition state for reaction of thiophene should occur earlier along the reaction coordinate than that for benzene. Thiophene will therefore stabilize more effectively the charge produced by an attacking electrophile, leaving less to be stabilized by the substituent. Although this has not been previously considered, it seems probable that variation in transition state structure is much greater in the latter class of reactions than in the former, and certainly the relative substituent effects appear to be quite different.

3. The transmission of charge through the heterocyclic ring. This may also lead to different results depending upon the degree of perturbation of the electronic structure of the ring, and again this has not been considered previously. Since the effects of substituents acting between the 2 and 5 positions parallels that acting between the 1 and 4 positions in benzene, it must follow that conjugative effects are involved, and this is confirmed by the correlation of appropriate data (below) with σ_p^+ values. Hence the transmission of conjugative effects must be largely *through the carbon chain*, and not through the heteroatom. It has been argued that as the aromaticity of a molecule decreases, the degree of conjugation will decrease, so that the electrons will be more mobile and the transmission should be better.[63] Put another way, **8** should be a better transmitter of electrons than **9**, because in **8** there will be a higher electron density on C_1 to be repelled by the lone pair on X than in **9**. Now while this is undoubtedly true for transmission across a 1,2 bond,

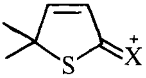


8



9

shown by the activating effects in hydrogen exchange of *ortho*-methyl, being 300 (1,2 interaction in naphthalene),[76] 305 (2,3 interaction in thiophene),[77,78] and 219 (1,2 interaction in benzene),[79] when a greater number of bonds are involved the converse applies. This is because in the fully delocalized structure **10** there is very



10

unfavorable bond fixation: bonds that are double in the ground state have become single, and vice versa. The ring bonds are therefore much more perturbed on going to the transition state than is the case in benzene. It seems likely, therefore, that the nearer the transition state is to the Wheland intermediate, the less thiophene will be able to transmit the conjugative effect of substituents relative to benzene. Thus the effect in hydrogen exchange of the methyl substituent acting through three bonds becomes 83 (1,4-interaction in naphthalene),[76] 200 (2,5-interaction in thiophene),[77,78] and 420 (1,4 interaction in benzene),[79] and clearly the situation has reversed relative to that noted above.

The importance of transmission factors vs. transition state charge has been stressed by various authors (e.g., Refs. 74 and 80), although the extreme view[80] that the amount of charge to be stabilized by the substituent is independent of the aromatic is considered unacceptable.[81]

Results suggest that in processes where a charge is formed in a side chain or is relatively small, then thiophene transmits substituent effects either the same as or better than benzene and less effectively than furan. It is less easy to decide here whether transmission is largely through the chain or the heteroatom, because although in molecules where transmission can take place *only* through the heteroatom, the transmission order is S > O,[82] the geometry of the heterocyclic ring brings additional factors into consideration. If inductive effects are important, then the shorter route through the heteroatom compared to –CH=CH– in benzene could contribute significantly to better transmission in the heterocycles. Furthermore, if there is a significant direct field component, then the 2,5 distance assumes greater significance than in an unconstrained system, and since this distance increases along the series furan < thiophene < (benzene), this will be the order of decreasing effectiveness of transmission. The following reactions appear to fall into this category.

The ionization of 5- and 4-substituted 2-thenoic acids were claimed to give higher and lower ρ factors, respectively, than for the benzoic acids;[68] however, a more recent determination shows the differences in ρ factors to be insignificant.[83] The ρ factor for the 5-substituted 3-thenoic acids was also stated to be higher than for the benzoic acids.[68] For the 5-substituted 2-tellurophenoic acids, the ρ factor is similar to that for the corresponding thiophene and selenophene compounds but less than for the furoic acids.[84] The ρ factors for hydrolysis of thenoic esters are greater than for the corresponding alkyl benzoates.[68] The carbonyl stretching frequencies in 5-*R*-2-acetylthiophenes correlate with σ^+ values;[67] this was confirmed in a more recent study on 1-phenyl-3-(5-aryl-2-heteroaryl)propenones, which showed that the transmission order was furan > thiophene > benzene.[72] Other studies by this method confirmed furan to be a better transmitter than benzene.[65] Measurement of the polarographic half-wave potentials have disagreed somewhat, the initial study indicating the order pyrrole > furan > thiophene ≈ benzene,[69] whereas a later study[64] gave the order as furan > thiophene > benzene. Solvolysis of 5-substituted 2-arylmethyl chlorides and *p*-nitrobenzoates (which also correlated with σ_p^+) gave ρ factors of −5.8 (benzene), −7.0 (thiophene), and −7.4 (furan).[74] CNDO/2 and INDO calculations in this latter study indicated that the difference in the charges in the ring in $ArCH_3$ and $ArCH_2^+$ was virtually the same at the 4 and 5 positions in thiophene as at the 3 and 4 positions in benzene; in furan, however, the charges at the corresponding positions were higher. The activating effect of a 5-methyl substituent in solvolysis of 1-(2-aryl)ethyl acetates decreased along the series furan > thiophene > benzene > selenophene > tellurophene.[60] A study of the sodium borohydride reduction of substituted 2-benzoylfurans and 2-benzoyl thiophenes had the advantage over the other studies in ensuring that the ring systems being compared were always stabilizing the same amount of charge. This study showed the transmission order to be furan = thiophene ≫ benzene.[71] Attention was drawn in this work to the possibility of steric hindrance to coplanarity between a side-chain cation and the aryl ring (which if present would be greatest in benzene) affecting the results. This would make benzene appear to have a lower transmission ability. The borohydride reduction results were considered to be unaffected by this, but other reactions described above might be, for example, solvolysis of 1-arylethyl esters. The reaction of aroyl chlorides with aniline required a higher ρ factor for the 2,5-interaction in thiophene than for the *para* interaction in benzene, by a factor of 1.22. (This is less than that quoted in Ref. 85, in which some data are misplotted and the correlation line did not pass through the origin.) Finally, a result that at first sight appears anomalous is the correlation of gas-phase ionization potentials with σ_p^+ giving ρ factors of 20.2 (furan), 18.2 (pyrrole), 16.5 (thiophene), and 14.7 (benzene).[73] This implies a very large conjugative interaction, so the intervention of bond-fixation effects should be apparent. However, the gas-phase ρ factors will be greatly affected by the absence of solvation (by a factor of approximately 5), making difficult direct comparison with the other data. Moreover, some of the correlations were poor; for example, the point for thiophene itself missed the correlation line by 0.2 sigma units.

For electrophilic substitutions, the indications are that bond-fixation effects are very important, so that in the majority of cases the ρ factor is greatest in the benzenes (Table 3). However, considerable doubt attaches to the accuracy of some of the ρ factors for the thiophenes, and only in acetylation, detritiation, and desilylation are the data at all reliable. It should be noted that acetylation of the thiophenes used $SnCl_4$ as a catalyst, whereas for the benzenes, $AlCl_3$, which is 500 times more effective, was used. If the same catalyst could have been used for both, the difference in ρ factors would probably be even greater than observed. For detritiation of benzenes, the ρ factor is −8.8[89] (not −8.2 as given in Ref. 3), and the value for the thiophenes is temperature-corrected to 70°C (the temperature of measurement used for the benzenes) via the Arrhenius equation. (Thiophene hydrogen-bonds in TFA/HOAc mixtures;[37] and in the presence of electron-supplying or -withdrawing substituents this bonding would be correspondingly greater or less,

TABLE 3. HAMMETT ρ FACTORS FOR ELECTROPHILIC SUBSTITUTION OF SUBSTITUTED BENZENES AND THIOPHENES

	ρ		
Reaction	Thiophene	Benzene	References
Bromination	−10.0	−12.1	86,87
Chlorination	ca. − 7.0	−10.0	44,87,88
Detritiation	− 6.5	− 8.8	70,89
Acetylation	− 5.6	− 9.1	90
Protiodesilylation	− 6.25	− 5.3	91
Mercuriation	ca. − 4.7[a]	− 4.0	44

[a] Mercuriation of substituted selenophenes is said to give $\rho = -5.7$ (Ref. 92). However, this was based on results for a few electron-withdrawing substituents only and did not include selenophene itself.

producing a diminished ρ factor. However, in the medium used for the detritiation study, bonding would be very small and unlikely to alter the ρ factor by more than 0.1 unit.) The ρ factor for desilylation of thiophene[91] does not take into account the effects of the 4- and 5-nitro substituents, which deactivate exceptionally for reasons described above.

For the other reactions, the ρ factors have been determined from data for only a few substituents (almost none of them electron-supplying), and including those—for example, CO_2Me and NO_2—that may deactivate exceptionally because the reduced steric hindrance in thiophene facilitates greater coplanarity with the thiophene ring. This has the effect of enhancing the ρ factors in thiophene, and this is convincingly demonstrated by the factors for individual substituents in chlorination[91] (the data provided by Marino[93] give the same result): Cl (−4.0); Br (−2.2); COOH (−9.4); COOEt (−8.0). Exactly the same result is observed in mercuriation and molecular bromination. The ρ factors for chlorination and mercuriation are probably not accurate to better than ±1.0 unit. The ρ factor for mercuriation of thiophene has been claimed to be anomalous because thiophene undergoes exclusive 2-substitution, implying a coordination step along the reaction pathway. However, no experimental details are available to substantiate this. There would seem to be a need for a thorough study of mercuriation and halogenation using a more representative range of substituents.

One would expect that the ρ factors for the thiophenes would be lower than for the benzenes if, as expected in view of the higher reactivity, the transition states for reaction are nearer to the ground state. Coupled with this would be the poorer conjugation in the heterocycle due to the bond-fixation factor. The results for bromination, chlorination, hydrogen exchange, and acetylation are in agreement with this. However, the difference between the ρ factors for the two systems seems to be substantially greater for acetylation than for the other reactions, while in protiodesilylation (and perhaps mercuriation) it is reversed. Two reasons may conceivably account for the large difference in acetylation. It is one of the most hindered of all electrophilic aromatic substitutions, so that approach of the electrophile to even