QUANTITATIVE ASPECT OF ELECTROPHILIC SUBSTITUTION IN FURAN, THIOPHENE, PYRROLE, AND OTHER FIVE-MEMBERED HETEROAROMATIC SYSTEMS (REVIEW)*

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Mechanism of Electrophilic Substitution in Five-Membered Rings

In most cases the mechanism of electrophilic substitution in five-membered heterocycles to a first approximation does not differ substantially from the generally accepted mechanism of substitution in homocyclic aromatic compounds [1], which assumes a change in the hybridization of the carbon atom under attack from sp^2 to sp^3 and the formation of particles (Wheland complexes or σ complexes) that are intermediates, i.e., they correspond to the minimum on the energy curve of the reaction. In most cases, the formation of a σ complex is the step that determines the reaction rate; in other cases, the structure of the substrate, the nature of the electrophilic agent, the experimental conditions, and the rate of conversion of the intermediate compound affect the reaction kinetics. In these cases, as was first demonstrated by Melander [2], one should expect the appearance of a positive primary isotope effect and an alkali catalysis effect.

A π complex (the aromatic ring is a donor) may form before (and probably after) the formation of the σ complex, although it has not been proved that the formation of the π complex is a necessary step of the reaction. An assumption was recently expressed [3] that if the electrophilic agent is very strong, the formation of a π complex may be the step that determines the rate of the overall reaction. This hypothesis is interesting and can be used in cases in which the aromatic compound is a strong nucleophile, such as pyrrole, for example.

A number of factors that complicate the occurrence of electrophilic substitution arise in the case of heteroaromatic substrates.

1. When there is a "basic" center (for example, the tertiary nitrogen atom in imidazole) present and substitution proceeds in strongly acid media, the substrate is protonated and substitution may occur in the conjugate acid, as, for example, in the nitration of imidazole and pyrazole [4]. Even in weaker acids (acetic acid, for example), the formation of hydrogen bonds with the nitrogen atom may change the orientation and reaction rate.

TABLE 1. Reactions of Five-Membered Heterocycles with Acetyl Trifluoroacetate*

Compound	Trifluoroacetyl derivative, %	Acetyl derivative, %
Thiophene	0,0	100
Furan	0,9	99,1
2-Methylthiophene	1,4	98,6
2-Methylfuran	15,9	84,1
Pyrrole	46,9	53,1
2-Methylpyrrole	91,9	8,1

* Reaction in dichloroethane at 75° [18].

2. When a secondary nitrogen atom is present (as in pyrrole or imidazole), the reaction may proceed

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TABLE 2. Relative Reactivities of Five-Membered Rings in Electrophilic Substitution

Compound	Acetylation*	Trifluoroacetylation†	Formylation‡	Bromination**
Thiophene	1	1	1	1
Selenophene	2,28	7,33	3,67	47,5
Tellurophene	7,55	46,4	36	—
Furan	11,9	140	103	120
Pyrrole	—	$5{,}3 \times 10^7$	—	$5{,}9 \times 10^8$

* Acetylation with acetic anhydride in the presence of stannic chloride [20, 21].

† Reaction with trifluoroacetic anhydride in dichloroethane [16, 22].

‡ Reaction with phosgene and dimethylformamide in chloroform [21].

** Relative rates of bromination (in the 5 position) of the 2-carbomethoxy derivatives in acetic acid [11,23, 24].

TABLE 3. Factors of the Partial Rates of Electrophilic Substitution Reactions in the Thiophene Ring [25]

No.	Reactions	ρ*	α_f	β_f
	Electrophilic substitution			
1	Bromination with Br_2	−12,1	$5{,}1 \times 10^9$	$1{,}05 \times 10^7$
2	Chlorination	−10,0	$3{,}9 \times 10^7$	$3{,}9 \times 10^5$
3	Acetylation	−9,1	$2{,}7 \times 10^6$	$1{,}35 \times 10^4$
4	Protodedeuteration	—	$8{,}7 \times 10^6$	$8{,}3 \times 10^3$
5	Protodetritiation	−8,2	$5{,}3 \times 10^6$	$5{,}8 \times 10^3$
6	Bromination with Br^+	−6,2	$1{,}9 \times 10^5$	$1{,}6 \times 10^3$
7	Nitration	—	$(7{,}1 \times 10^2)$	$(1{,}15 \times 10^2)$
8	Protodeboration	—	$8{,}5 \times 10^5$	$7{,}1 \times 10^3$
9	Iododeboration	−4,8	$9{,}7 \times 10^3$	$7{,}0 \times 10^2$
10	Protodesilylation	−4,6	$5{,}0 \times 10^3$	$1{,}15 \times 10^2$
11	Mercuration	−4,0	$1{,}85 \times 10^6$	—
12	Protodemercuration	−2,4	$1{,}7 \times 10^3$	—
	Reaction of carbonium ions in the side chain			
13	Solvolysis of 1-arylethyl p-nitrobenzoates	−6,0	$6{,}3 \times 10^4$	1×10^3
14	Solvolysis of 1-arylethyl acetates	−5,7	$5{,}4 \times 10^4$	$4{,}8 \times 10^2$
15	Isomerization of cis-1-aryl-2-phenylethenes	−3,3	$3{,}5 \times 10^2$	—
16	Rearrangement of arylphenylcarbinols	−2,9	50,2	—
17	Pyrolysis of 1-arylethyl acetates	−0,66	3,3	1,8

* These are the ρ constants for benzene derivatives: L. M. Stock and H. C. Brown, Adv. Phys. Org. Chem., 1, 35 (1963).

through the anion formed during dissociation to give products of substitution either at the nitrogen atom or at the carbon atom. For example, both 1-acetyl- and 2-acetylpyrrole are formed in the reaction of pyrrole with acetic anhydride at 130°C [5]. It should be assumed that substitution at C(α) proceeds in the neutral molecule, while substitution at the nitrogen atom occurs in the anion that is formed during dissociation. This is confirmed by the fact that the C/N ratio of the isomers decreases when sodium acetate (which increases ionization) is added and increases when acetic acid is added.

Another example of substitution through the conjugate base is the azo coupling of imidazole [6], in which the 2 isomer is usually formed. However, if the reaction is carried out in acid media, the 4 isomer is formed.

3. In some cases the heteroaromatic ring can form a different sort of complex (p donors, with charge transfer, etc.) with the electrophilic agent or catalysts. For example, an orange complex of the bromonium ion was isolated in the bromination of imidazole in chloroform [7]. Another example of this sort of complication of the process is the mercuration of thiophene [8]. The research that is currently being conducted in our laboratory shows that the mercuration of thiophene proceeds via a mechanism that differs from the

TABLE 4. Factors of the Partial Rates of Electrophilic Substitution Reactions in the Furan Ring [28, 29]

Reactions	ρ^*	α_f	β_f
Electrophilic substitution			
Bromination	−12,1	$6{,}1\times10^{11}$	—
Chlorination	−10,0	$1{,}9\times10^{9}$	—
Acetylation	−9,1	$3{,}2\times10^{7}$	2×10^{4}
Protodesilylation	−4,3	$1{,}7\times10^{4}$	$1{,}17\times10^{2}$
Protodemercuration	−2,4	$4{,}0\times10^{3}$	$1{,}5\times10^{2}$
Reactions of carbonium ions in the side chain			
Solvolysis of 1-arylethyl p-nitrobenzoates	−6,0	$1{,}0\times10^{5}$	$2{,}9\times10^{2}$
Solvolysis of 1-arylethyl acetates	−5,7	$2{,}1\times10^{5}$	$6{,}7\times10^{2}$
Rearrangement of arylphenylcarbinols	−2,9	90	—
Pyrolysis of 1-arylethyl acetates	−0,66	3,8	1,9

TABLE 5. Relative Reactivities of Selenophene and Thiophene and Factors of the Partial Rates of Substitution in the Selenophene Ring [24]

Reactions	ρ^*	Ratio of the rates of substitution of selenophene and thiophene	α_f
Bromination with Br_2	−12,1	47,5	$2{,}4\times10^{11}$
Chlorination	−10,0	6,5	$2{,}5\times10^{8}$
Acetylation	−9,1	1,9	$5{,}1\times10^{6}$
Protodedeuteration	(−8,5)	11	$9{,}6\times10^{7}$
Bromination with Br^+	−6,2	4,5	$8{,}5\times10^{5}$
Trifluoroacetylation	—	6,6	—
Protodemercuration	−2,44	2,2	$3{,}7\times10^{3}$

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*These are the ρ constants for benzene derivatives: L. M. Stock and H. C. Brown, Adv. Phys. Org. Chem., 1, 35 (1963).

mechanism of the mercuration of benzene and includes prior coordination of mercury at the sulfur atom.

In some cases the substrate reacts with the catalyst. The reaction does not proceed when pyrrole is treated with acetic anhydride with a catalytic amount of stannic chloride at room temperature [5]. Under these same conditions, furan and thiophene (which are less reactive during electrophilic substitution) readily give the acetyl derivatives. It follows from this that stannic chloride forms a stable complex with pyrrole and does not catalyze the formation of electrophilic particles from the anhydride. This assumption is confirmed by the fact that furan and thiophene also lose their capacity for acetylation in the presence of pyrrole [5].

4. Since the double bonds in a heteroaromatic system are fixed to a considerable degree, substitution may be accompanied by the addition of an electrophilic agent. For example, 2-acetoxy-5-nitro-2,5-dihydrofuran is formed in the nitration of furan in acetic anhydride.

5. The existence of prototropic equilibria superimposed other complexities. One should have in mind two types of tautomerism: in the heteroring itself (indole-indolenine and pyrrole-pyrrolenine) and tautomerism peculiar to hydroxy and amino derivatives. Substitution may occur, at least theoretically, in the prototropic nonaromatic form.

This reasoning regarding the peculiarities and differences does not exclude the fact that substitution in five-membered heterorings in most cases proceeds similarly to the reactions in the benzene series. This is particularly the case for thiophene, which is closest in chemical behavior to benzene. For example, bromination of thiophene in acetic acid proceeds in analogy with bromination of benzene compounds [10, 11], i.e., a complex pattern is observed, and the reaction order in bromine lies between one and two. Moreover, the bromination of thiophene, like that of benzene derivatives, in the presence of lithium bromide is a second-order reaction with respect to bromine (first-order with respect to each reagent). The same effect of the percentage of water in the solvent, the ionic strength of the solution, the bromide ion concentration, and the

TABLE 6. Constants for Heteroatoms as Substituents

Heteroatom	σ_α^+	σ_β^+
O	−0,93	−0,44
S	−0,79	−0,52
Se	−0,88	—
Te	−0,91	—
NH	−1,53	—

effect of substituents in the aromatic system are observed in the bromination of thiophene and benzene derivatives. This confirms the similarity between the mechanisms of the reactions in both cases. The kinetic isotope effect and the Arrhenius parameter have the same values in the bromination of thiophene and benzene derivatives [13]. The chlorination of thiophene [10] proceeds via the same mechanism as in the chlorination of benzene. Hydrogen exchange in thiophene, furan, and benzene proceeds via the same mechanism [14]. The increased reactivity of these systems as compared with electrophilic agents makes it possible to conduct a quantitative investigation of the interaction with electrophiles of medium strength, with which benzene does not react. The kinetics of formylation of thiophene derivatives via the Vilsmeier reaction have been investigated [15]. The formylation of thiophene and methylthiophenes in dichloroethane proceeds via a third-order scheme (first-order in substrate, phosphorus oxychloride and dimethylformamide). More reactive substrates (such as 2-methoxythiophene) are formylated via a second-order scheme, and the rate of substitution of them is independent of the substrate concentration. The mechanism includes equilibrium (a), which leads to the formation of an electrophilic agent, and subsequent attack of it on the substrate (b) to give an intermediate, which is then converted to the final aldehyde by the action of water:

$$\text{Dimethylformamide} + POCl_3 \rightleftharpoons \text{complex} \qquad (a)$$

$$\text{complex} + \text{thiophene} \rightarrow \text{intermediate} \qquad (b)$$

$$\text{intermediate} + 3H_2O \rightarrow C_4H_3SCHO + (CH_3)_2\overset{+}{N}H_2\overset{-}{Cl} + H_3PO_4 + 2HCl$$

Step (b) is the determining step in the formylation of thiophene and methylthiophenes; in the case of 2-methoxythiophene, step (b) proceeds very rapidly and step (a) (formation of the complex) becomes the kinetically determining step. If phosgene is used in place of phosphorus oxychloride, equilibrium (a), because of the evolution of carbon dioxide, is shifted completely to the right, and crystalline complex $[(CH_3)_2NCHCl]^+$-Cl^- is formed. This complex was isolated, and its reaction with heteroaromatic compounds is clearly a second-order reaction – first-order in substrate and first-order in complex.

Trifluoroacetylation with trifluoroacetic anhydride in an inert solvent [16] is another reaction with electrophiles of medium strength that was studied in our laboratory. Trifluoroacetylation is interesting for several reasons. First, all of the investigated heterocyclic compounds (including pyrrole) are converted to monotrifluoroacetyl derivatives without the appreciable formation of side products. Second, this is an acylation reaction that does not require Friedel–Crafts catalysts,and the complications that arise during the reaction of some heterocycles with such catalysts [5] are excluded. Finally, this selective reaction is exceptionally convenient for a comparison of the structure and reactivity. Another interesting acylating agent that does not require a catalyst is the mixed anhydride of acetic and trifluoroacetic acids, which is frequently called acetyl trifluoroacetate. Acetyl trifluoroacetate is described as an acetylating agent in the literature. For example, anisole and phenetole react with it to give exclusively methoxy (or ethoxy)acetophenone [17]. However, we have shown that five-membered heterocycles react with acetyl trifluoroacetate to give mixtures of acetylated and trifluoroacetylated products, the composition of which depends on the reactivity of the substrate and the experimental conditions [18, 19]. The ratio of the products of the reactions in 1,2-dichloroethane at 75° is presented in Table 1. It is seen from the data in Table 1 that the amount of trifluoroacetyl derivative increases as the reactivity of the substrate increases. Thiophene and 2-methylpyrrole are the boundary cases: the first gives exclusively 2-acetylthiophene, while the second gives more than 90% of the 5-trifluoroacetyl derivative. Raising the temperature and polarity of the solvent and the addition of Lewis acids promote the acetylation, while the addition of lithium trifluoroacetate leads to an increase in the yield of the trifluoroacetyl derivative. On the basis of the data presented, a comparison of the reactivities and selectivities with respect to other electrophilic agents, it can be assumed [19] that trifluoroacetylation proceeds under the influence of the undissociated anhydride, while acetylation proceeds under the influence of the acetylium ion (CH_3CO^+, as the free cation or as an ion pair).

Relative Reactivities of Five-Membered Heterocycles

At the outset of our investigations, the literature contained no quantitative comparative data on the reactivities of the principal five-membered heterocycles. In textbooks on organic chemistry there was not even agreement on the qualitative reactivities.

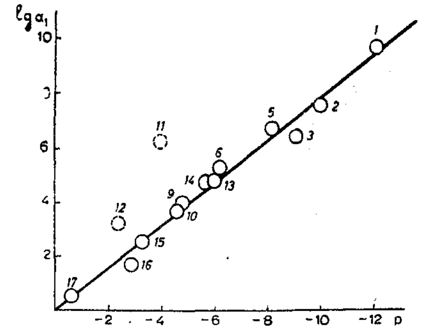

Fig. 1. Extended selectivity ratio for electrophilic substitution reactions in the α position of the thiophene ring (the reactions presented in Table 3 are designated by the numbers beside the points).

The principal five-membered heterocycles are presently arranged in the order of their reactivities on the basis of kinetic data or thorough comparative experiments. The ratio of the reactivities of furan, thiophene, selenophene, tellurophene, and pyrrole in four electrophilic substitution reactions (acetylation, trifluoroacetylation, Vilsmeier formylation, and bromination) is presented in Table 2. The high reactivity of pyrrole cannot be ascribed to the formation of the $C_4H_4N^-$ anion, since N-methylpyrrole (for which the formation of such an ion is impossible) is even more reactive than pyrrole.

Since the ratio of the rates of bromination of thiophene and benzene is known [10], it becomes possible to calculate the partial rates of bromination (with respect to one position in benzene) of the α position of the principal heterocycles: thiophene $5 \cdot 10^9$, selenophene $2.4 \cdot 10^{11}$, furan $6 \cdot 10^{11}$, and pyrrole $3 \cdot 10^{18}$. These data, although they are approximate, are a unique comparison of the reactivities of five-membered heterocycles and benzene.

Alpha:Beta Ratio. It is well known that electrophilic attack is directed to the α position more readily than to the β position in all five-membered heterocycles; this can be explained by a comparison of the energies of the transition states for α and β substitution. The isomer distribution and the reactivity ratio of the α and β positions depend markedly on the electrophilic agent and the experimental conditions (for example, the temperature); basically, the lower the strength of the electrophilic agent, the higher the α:β ratio [25]. This ratio also depends to a considerable extent on the heteroatom. Although there have been no comparative investigations under identical conditions, the available data nevertheless basically confirm the following order with respect to orientation in the α position: furan > thiophene ≃ selenophene ≫ pyrrole. This difference in the α:β ratio observed for the four heterocycles may be due to many reasons. The especially small α:β ratio for pyrrole (as well as the low sensitivity of the ring to substituents) is possibly explained by the fact that the Wheland complex is not a satisfactory model for the transition state.

Partial Rates and Expanded Selectivity Ratio

The isomer ratio and the relative rates of substitution make it possible to calculate the partial rates (the partial rate is the rate of substitution of one position in the heteroaromatic ring with respect to one position in benzene). The partial rates obtained for electrophilic substitution are presented in Tables 3 (thiophene), 4 (furan), and 5 (selenophene). Data pertaining to reactions in the side chain, when a resonance-stabilized carbonium ion is formed, are included in the tables. In a certain respect, these reactions recall electrophilic substitution and are frequently used for the determination of the reactivities of aromatic compounds. The partial rates vary over wide limits for the same ring. Electrophilic agents of low activity such as molecular bromine are more selective, i.e., either different rings or the α and β positions in the same ring are more readily "distinguished." Quantitatively, a linear dependence of log α/β on log α_f is observed. This correlation is formally analogous to the selectivity ratio proposed by Brown and Nelson [26] for the reactions of monosubstituted benzenes.

The data in Tables 3-5 can be used to demonstrate the linear ratios of the free energies of electrophilic reactions in five-membered heterocycles. The extended method of selectivities [27] can be used for the successful solution of the problem. According to this method (which is the inverse Hammett method), the substrate remains the same, but the log k/k_0 values are correlated with ρ for different reactions. A satisfactory linear correlation between log α_f or log β_f (for substitution in thiophene [25], furan [28, 29], and selenophene) and the ρ values obtained from the data of analogous reactions of benzene derivatives is obtained. An example of the application of the extended selectivity method to reactions of the α position of thiophene is presented in Fig. 1. Nitration and protodeboration are not presented, since in the case of thiophene these reactions proceed under conditions that differ from those that were used to calculate ρ. Two chief deviations – mercuration and protodemercuration – which differ substantially from what the ratio predicts, can be observed in Fig. 1. This is not surprising, since, as noted above, mercuration of thiophene proceeds via a mechanism that differs from the mechanism of the mercuration of benzene, probably through prior coordination of mercury on the sulfur atom. The data from the rest of the reactions follow the linear expression very well. This linear dependence points out the similarity between the mechanisms of electrophilic substitution of heteroaromatic and benzene derivatives.

TABLE 7. Electrophilic Substitution and Related Reactions in Furan, Thiophene, Benzofuran, and Benzothiophene. Relative Partial Rates [30]

Reactions	(β-Thiophene	β-Furan	β-Benzofuran	α-Benzothiophene	β-Benzothiophene	α-Benzofuran	α-Thiophene	α-Furan
Bromination, Br_2, AcOH, 25°C	1	—	—	2,07	189	—	490	(58,800)*
Chlorination, Cl_2, AcOH, 25°C	1	—	—	2,90	126	—	100	(5,000)*
Bromination, HOBr, $HClO_4$, 50% dioxane, 25°	1	—	—	0,16	12,1	—	120	—
Benzoylation, Br_2O, $SnCl_4$, dichloroethane, 75°	1	2,43	2,97	6,66	12,8	25,0	65,6	609
Acetylation, Ac_2O, $SnCl_4$, dichloroethane, 25°	1	2,40	1,78	2,00	13,3	12,9	500	2,380
Acetylation, acetyl trifluoroacetate, dichloroethane, 75°	1	0,71	1,86	3,57	13,3	14,8	71,4	704
Protodeuteration [31], CF_3COOH, AcOH, 25°	1	—	—	6,25	10,0	—	3,000	—
Protodesilylation, $HClO_4$, CH_3OH, 50°	1	1,02†	—	0,35	0,36	—	42,8	153
Solvolysis of 1-arylethyl p-nitrobenzoates‡	1	0,84	2,06	1,27	3,43	2,06	62,1	293
Solvolysis of 1-arylethyl acetates**	1	1,41	0,87	0,69	2,14	1,04	113	448

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* Data for 2-carbomethoxy derivative.

† R. Taylor, J. Chem. Soc., B, 1364 (1970).

‡ D. S. Noyce, private communication.

** E. A. Hill, M. L. Gross, M. Stasiewicz, and M. Manion, J. Am. Chem. Soc., 91, 7381 (1969).

TABLE 8. Effect of "Annelation" on the Reactivities of the α and β Positions of Furan and Thiophene

Reactions	α-Benzofuran / α-furan	β-Benzofuran / β-furan	α-Benzothiophene / α-thiophene	β-Benzothiophene / β-thiophene
Bromination, Br_2, AcOH, 25°	—	—	$4,2\times10^{-3}$	189
Chlorination, Cl_2, AcOH, 25°	—	—	$2,9\times10^{-2}$	126
Bromination, HOBr, $HClO_4$, aqueous dioxane, 25°	—	—	$1,3\times10^{-3}$	12,1
Acetylation, Ac_2O, $SnCl_4$, dichloroethane, 75°	$1,3\times10^{-2}$	>3,6	$3,0\times10^{-2}$	9,1
Acetylation, acetyl trifluoroacetate, dichloroethane, 75°	$2,1\times10^{-2}$	>2,6	$5,0\times10^{-2}$	13,3
Benzoylation, Br_2O, $SnCl_4$, dichloroethane, 75°	$4,1\times10^{-2}$	1,22	$1,0\times10^{-1}$	12,8
Protodedeuteration, CF_3CO_2H, AcOH, 25°	—	—	$2,0\times10^{-3}$	10,0
Protodesilylation, $HClO_4$, CH_3OH, 50°	—	—	$8,2\times10^{-3}$	0,36
Solvolysis of 1-arylethyl acetates, 25°	$2,3\times10^{-3}$	0,62	$6,1\times10^{-3}$	2,1
Solvolysis of 1-arylethyl-p-nitrobenzoates, 75°	$7,0\times10^{-3}$	2,53	$2,0\times10^{-2}$	3,4

From the slopes of these lines, one can calculate the substituent constants (σ^+) relative to the structural changes caused by substitution of the CH = CH group in the benzene ring by the heteroatom. The σ^+ constants of the heteroatoms are presented in Table 6.

Reactivities of Monobenzo Derivatives

The different orientation in substitution in benzofuran and benzothiophene is surprising. Benzofuran, like furan, is substituted mainly in the α position, while benzothiophene is substituted primarily in the β position. The qualitative literature data are confirmed by the thorough quantitative determination of the isomer ratio under strictly controlled conditions [30]. The α:β ratio depends markedly on the nature of the electrophilic agent and the experimental conditions [30]. The relative rates of electrophilic substitution with respect to the starting heterocycles are determined by using competitive reactions and accurate kinetic measurements.

The relative rates and the isomer ratios made it possible to calculate the partial rates of different nonequivalent positions of these systems (Table 7). By taking into account the deviation and even the lines

TABLE 9. Relative Rates of α-Substitution of Thiophenes [12, 29-32]*

Substituent	Bromination	Chlorination	Detritiation	Dedeuteration	Acetylation	Trifluoroacetylation	Mercuration
2-OCH_3	—	—	—	$1{,}5\times10^{6}$	—	$1{,}8\times10^{6}$	—
2-SCH_3	—	—	—	$1{,}5\times10^{3}$	—	$5{,}2\times10^{3}$	—
2-CH_3	$6{,}3\times10^{2}$	—	$2{,}1\times10^{2}$	$2{,}3\times10^{2}$	35,2	$3{,}8\times10^{2}$	—
2-C_2H_5	—	—	—	—	—	$5{,}2\times10^{2}$	—
2-tert-C_4H_9	—	—	$2{,}3\times10^{2}$	—	52,9	$5{,}4\times10^{2}$	—
2-C_6H_5	—	—	15,5	—	—	$1{,}1\times10^{2}$	—
3-CH_3	—	—	—	12	2,95	—	—
H	1	1	1	1	1	1	1
2-Cl	$5{,}2\times10^{-1}$	0,42	$1{,}7\times10^{-1}$	—	0,14	$5{,}8\times10^{-1}$	—
2-Br	$3{,}8\times10^{-1}$	0,33	$1{,}3\times10^{-1}$	—	—	$4{,}6\times10^{-1}$	$2{,}6\times10^{-1}$
2-I	$(9{,}4\times10^{-1})$	0,53	$1{,}9\times10^{-1}$	—	—	—	—
3-SCH_3	—	—	—	0,1	—	—	—
2-$COCH_3$	—	—	—	—	—	—	$2{,}8\times10^{-3}$
2-CO_2H	$3{,}3\times10^{-5}$	$1{,}1\times10^{-4}$	—	—	—	—	—
2-$CO_2C_2H_5$	$1{,}1\times10^{-5}$	$1{,}3\times10^{-4}$	—	—	—	—	$3{,}4\times10^{-3}$
2-NO_2	—	$1{,}1\times10^{-6}$	—	—	—	—	—

*Substitution in the 5 position of the thiophene ring.

TABLE 10. Constants for Substitution Reactions in the Benzene and Thiophene Rings [12, 32, 34-36]

Reactions	Thiophene	Benzene
Bromination	−10,0	−12,1
Chlorination	−7,8	−10,0
Protodeuteration	−7,6	—
Protodetritiation	−7,2	−8,2
Acetylation	−5,6	−9,1
Trifluoroacetylation	−7,4	—
Mercuration	−5,3	−4,0

of nonconformity, one can present the following order of relative reactivities: β-furan ≤ β-thiophene < β-benzofuran ≃ α-benzothiophene < β-benzothiophene ≃ α-benzofuran ≪ α-thiophene ≪ α-furan.

Data on the effect of "annelation" on the reactivities of the α and β positions of the furan and thiophene rings are presented in Table 8. The data are somewhat unexpected. Despite the fact that the orientation of substitution in both two-ring systems is different, the effect of a condensed benzene ring is identical. The reactivities of the α positions in all cases are reduced, while the reactivities of the β positions (except for two cases) are increased. Hence it can be concluded that the different orientation observed in the two-ring systems is not a consequence of condensation with the benzene ring but rather is a consequence of the different α:β ratio in the two one-ring systems [30].

The literature does not contain quantitative data on electrophilic substitution in indole. However, it is known that the α:β ratio in pyrrole is considerably lower than in furan and thiophene. Consequently, if the effect of "annelation" remains the same as in furan and thiophene, it can be expected that the β position in indole will be considerably more reactive, and this is actually observed.

Effect of Substituents on Orientation

The 2 and 5 positions of the heterocycles are in conjugation like the para positions in benzene, and resonance interaction of the reaction center in the 5 position with the substituent in the 2 position is therefore possible. The 2 and 4 positions are positions of the meta type, between which resonance interaction is impossible. If there are ortho-para orienting groups in the 2 position, substitution proceeds in the 5 position, which is the α position with respect to the heteroatom and the para position with respect to the substituent. If a meta-orienting substituent is in the 3 position, substitution always occurs in the 5 position, i.e., in the α position with respect to the heteroatom and the meta position with respect to the substituent.

If there is a m-orienting substituent in the 2 position, competition arises between the orienting effects of the heteroatom and the substituent. In furan (and, in particular, in thiophene), for which the α:β ratio is very large, the α-orienting effect of the heteroatom prevails, and substitution proceeds mainly in the 5 position. In pyrrole, in which the $\alpha:\beta$ ratio is low, a mixture of isomers with, as a rule, predominance of the 4 isomer is formed.

Linear Correlations of Free Energies

The relative rates of substitution in the thiophene series are currently known for several reactions: bromination with molecular bromine [12], chlorination with molecular chlorine [32], acetylation in the presence of stannic chloride [32], protodetritiation [34], acetoxymercuration [36], protodedeuteration [35], and trifluoroacetylation [32, 33]. There are enough of these reactions to trace the applicability of the $\rho\sigma^+$ ratios (Table 9).

A comparison of the ρ values for the thiophene and benzene series is made in Table 10. In all cases, ρ in the thiophene series has a somewhat lower value (in absolute magnitude) than in the benzene series. The only exception to this is mercuration, which, as was pointed out above, probably proceeds via a different mechanism. A possible explanation for this is the fact that thiophene is more reactive then benzene, the transition state comes after the Wheland structure, and in this case relatively less positive charge is concentrated on the ring. We later compared the sensitivity of the furan, thiophene, and pyrrole rings to the effect of a substituent during trifluoroacetylation. The relative rates (with respect to the unsubstituted heterocycle) of 18 substituted furans, thiophenes, and pyrroles were determined by the method of competitive reactions.

It is seen from these data that the sensitivity to the substituent effect falls in the order furan > thiophene > pyrrole. It is interesting that the order of "substrate" selectivity during trifluoroacetylation coincides with the order of "position" selectivity, since, as shown above, the $\alpha:\beta$ ratio falls in the same order, i.e., furan > thiophene > pyrrole.

This fact confirms the hypothesis that the transition state during substitution in furan most closely approaches a Wheland complex, while the transition state for pyrrole is far removed from the σ complex and has more pronounced π character. Preliminary data on other electrophilic substitution reactions confirm the validity of this conclusion.

We note that the same tendency (i.e., the sensitivity of furan to substituents is the greatest among the five-membered heterocycles) was observed during molecular ionization in the gas phase [37, 38], in a reaction that, in a certain respect, can be considered to be similar to electrophilic substitution reactions [39].

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