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RELATIVE REACTIVITIES OF SOME FURAN AND THIOPHENE DERIVATIVES IN THE IODINE- AND TIN TETRACHLORIDE-CATALYSED ACETYLATIONS WITH ACETIC ANHYDRIDE IN DICHLOROETHANE[1]

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Abstract—The reactivities of furan and thiophene in the catalysed acetylation by acetic anhydride, have been compared using a competitive procedure. Furan is more reactive than thiophene by a factor 9·3 or 11·9 according to the catalyst used (iodine or tin tetrachloride, respectively). This appears to be the first quantitative comparison of the reactivities of these two heterocyclic rings in an electrophilic substitution in which a proton is displaced.

The rates of acetylation of 2-methylthiophene, 2-chlorothiophene and anisole relative to thiophene have been also determined and discussed.

A COMPARISON of the aromatic character of thiophene, furan and pyrrole rings among themselves and with benzene, is often confusing in that many authors describe the 5-membered heterocyclic rings as "less" aromatic than benzene, others refer to them as having "superaromatic" or "hyperaromatic" properties.

The problem, as has been pointed out,[2] is due to two distinct concepts, i.e. "ground state aromaticity" and "aromatic reactivity", the latter depending also on the energy of the transition state for the chemical reaction involved.

For the *ground state aromaticities* there are basically two different criteria for a quantitative comparison: one based on the resonance energy and the other, recently proposed,[3] based on the magnitude of the "ring current", as measured by the degree of shielding of the protons attached to the aromatic nucleus.

According to the resonance energy criterion, the aromaticity order is the following:[4] benzene (36 Kcal/mole) $>$ thiophene (ca. 30) $>$ pyrrole (ca. 23) $>$ furan (ca. 21). The same qualitative order was obtained by applying the induced ring current criterion based on the measurement of the PMR chemical shifts.[5,6] Other authors, however, applying this method, arrived at somewhat different conclusions.[7,8]

As regards the *aromatic reactivities* of these systems, very few data are available for a quantitative comparison. Even the qualitative order of reactivity towards electrophiles, as deduced from preparative chemical data, is not definitively established.

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[1] This paper is part III of the series: Electrophilic Substitutions in five-membered heterocyclic systems—Part II: G. Marino, *Atti Acc. Naz. Lincei*, **38**, 700 (1965).

[2] D. Peters, *J. Chem. Soc.* 1274 (1960).

[3] J. A. Elvidge and L. M. Jackman, *J. Chem. Soc.* 859 (1961).

[4] R. M. Acheson, *An introduction to the chemistry of heterocyclic compounds* p. 122. Interscience, N.Y. (1962).

[5] J. A. Elvidge, *Chem. Comm.* 160 (1965).

[6] H. A. P. de Jongh and H. Wynberg. *Tetrahedron* **21**, 515 (1965).

[7] R. J. Abraham, R. C. Sheppard, W. A Thomas and S. Turner, *Chem. Comm.* 43 (1965).

[8] R. J. Abraham and W. A. Thomas, *J. Chem. Soc.* (B), 127 (1966).

The order more frequently reported is: benzene < thiophene < furan < pyrrole, although a different one is reported by some other excellent textbooks.[9]

The only quantitative measurement of relative reactivities refers to the protodesilylation of the 2-trimethylsilyl derivatives of furan and thiophene:[10] the 2-position of furan appears to be about four times as reactive as the 2-position of thiophene. However, data concerning the electrophilic substitution of a proton in the unsubstituted rings are completely lacking.

The lack of quantitative data is in part due to the fact that, under the conditions used for electrophilic substitution, i.e. in the presence of mineral acids, unsubstituted furan and pyrrole rings undergo ring-cleavage and/or polymerisation.

We have found that certain acylations, under properly chosen conditions, are suitable for a quantitative comparison of reactivity of thiophene and furan rings towards electrophiles.

The use of acetic anhydride is preferable to acetyl chloride since a weaker acid is liberated in the course of the reaction. Aluminium trichloride is not a good catalyst since it induces polymerisation of furan derivatives.[11] Iodine[12] and tin tetrachloride[13,14] were chosen as catalysts as they have been used successfully in the synthesis of ketone derivatives of furan and thiophene. 1,2-Dichloroethane was selected as the solvent since it is particularly suitable for Friedel-Crafts acylations.[15]

In the present paper we report the determination of the relative rates of the iodine- and the tin tetrachloride-catalysed acetylations of furan, thiophene and some α-substituted thiophene derivatives. Unfortunately, benzene is unreactive under the conditions mentioned and, therefore, we could not make a direct comparison of reactivity between it and the 5-membered heterocycles. However, we have measured the relative rates for a more reactive mono-substituted derivative of benzene—anisole.

Unfortunately, the extension of this study to pyrrole derivatives gave rise to complications which will be reported in a subsequent note. The reactivity of the pyrrole ring relative to that of furan and thiophene in other substitutions is now being investigated.

RESULTS AND DISCUSSION

Examination of the reaction products. Each of the examined substances was first individually treated in dichloroethane with a solution containing the acetic anhydride and the catalyst (in the molar ratio 100:1). The reactions were allowed to go to completion and, after hydrolysis, the products were examined by VPC.

It has been reported that the acetylation of thiophene, furan, 2-methyl- and 2-chlorothiophene yields the corresponding *alpha*-acetylderivative, exclusively.[12–14,16,17] Similarly, *p*-methoxyacetophenone was reported to be the sole product of acetylation

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[9] See, for instance, J. D. Roberts and M. C. Caserio, *Basic principles of organic chemistry* p. 987. W. A. Benjamin, New York (1964).

[10] C. Eaborn and J. A. Sperry, *J. Chem. Soc.* 4921 (1961).

[11] A. P. Dunlop and F. N. Peters, *The Furans* p. 64. Reinhold, New York (1953).

[12] H. D. Hartough and A. I. Kosak, *J. Am. Chem. Soc.* **68**, 2639 (1946).

[13] M. W. Farrar and R. Levine, *J. Am. Chem. Soc.* **72**, 4433 (1950).

[14] Ya L. Gol'dfarb and L. M. Smorgonskii, *J. Gen. Chem. USSR*, **8**, 1523 (1938), *Chem. Abstr.* **33**, 4593 (1939).

[15] F. R. Jensen, G. Marino and H. C. Brown, *J. Am. Chem. Soc.* **81**, 3303 (1959).

[16] H. D. Hartough and A. I. Kosak, *J. Am. Chem. Soc.* **69**, 3093 (1947).

[17] W. S. Emerson and T. M. Patrick Jr., *J. Org. Chem.* **13**, 722 (1948).

of anisole.[18] Actually, the V.P. chromatograms of the reaction products of furan, thiophene and 2-chlorothiophene exhibited only a sharp peak and no trace of other isomers was detected.

In the reaction mixtures of anisole and 2-methylthiophene, in addition to the major product, minor components were observed which had a shorter retention time and probably were *ortho*-methoxyacetophenone and 2-methyl-3-acetylthiophene, respectively. However, in view of their amount (less than 5%) we did not consider it necessary to give definitive proof of their structure.

The total yields were established by adding an internal standard to the reaction mixtures. Whereas for thiophene derivatives, the conversions were practically quantitative, for furan they were somewhat smaller (81% in the iodine, and 90% in the tin tetrachloride-catalysed reaction). Probably polymerisation occurred under the reaction conditions with formation of some high-boiling materials.

It should be noted, however, that the figure for the iodine-catalysed reaction refers to an experiment carried out at 70° since the reaction at 25° was too slow to go to completion in a reasonable interval of time. It is therefore probable that, at the lower temperature used for the competitive experiments (25°) the percentage of decomposition was much smaller. In any case, the percentage of decomposition was not so high as to alter substantially the conclusions derived from the competitive experiments.

Determination of the relative rates. The relative rates were measured using the competitive method, originally developed by Ingold.[19] This method, when compared with the kinetic method, has the advantage of not requiring a complete knowledge of the reaction kinetics and has been used successfully by many authors in the field of aromatic electrophilic substitutions.[20–22] Also it has the advantage, particularly important in connection with the present study, that the actual concentration of the reactive species does not need to be known.

Suitable mixtures of two or three aromatic substrates in ethylene dichloride were treated with a solution containing the acetic anhydride and the catalyst in the molar ratio 100:1. The molar concentration of the anhydride was always kept lower than that of each aromatic substrate.

All the reactions examined were slow enough to avoid determination of the product ratios by diffusion rather than by kinetic factors.[23]

The reaction solutions were allowed to stand at 25° long enough to reach percentages of 20–40%, then quenched and analysed by VPC. (See Experimental.)

The molar ratio of the resulting ketones enabled the relative rates to be calculated by using the appropriate formula.[24] They are summarized in Table 1.

As the above formula can be employed for the determination of relative rates only

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[18] S. Chodroff and H. C. Klein, *J. Am. Chem. Soc.* **70**, 1647 (1948).

[19] C. K. Ingold and F. R. Shaw, *J. Chem. Soc.* 2918 (1927).

[20] M. J. S. Dewar, T. Mole and E. W. T. Warford, *J. Chem. Soc.* 3576 (1956); M. J. S. Dewar and D. S. Urch, *Ibid.* 3079 (1958).

[21] H. C. Brown, G. Marino and L. M. Stock, *J. Am. Chem. Soc.* **81**, 3310 (1959); G. Marino and H. C. Brown, *Ibid.*, **81**, 5929 (1959).

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[23] W. S. Tolgyesi, *Canad. J. Chem.* **43**, 343 (1965).

[24] G. A. Russell, *Competing reactions* in A. Weissberger, *Investigations of rates and mechanisms of reactions* (2nd Edition) Vol. 1; p. 344. Interscience, New York (1961).

TABLE 1. RELATIVE RATES OF ACETYLATION BY ACETIC ANHYDRIDE AT 25°

Substrate	k/k_0(I_2-catald.)	k/k_0($SnCl_4$-catald.)
Anisole	0·377	0·320
2-Chlorothiophene	0·080	0·0714
Thiophene	1	1
2-Methylthiophene	15·6	17·6
Furan	9·33	11·9

if the reactions are of the first order with respect to the substrate, the following experiments were made:

(1) The absolute and relative concentrations of the reactants were changed over a wide range. The relative rates remained constant within the experimental errors (Table 2).

(2) Competitive acetylations were carried out with mixtures of three substrates. The results did not differ from those derived from binary mixtures (Table 2). If the kinetics were complicated by rapid preequilibria between the substrate and the reagent, then the relative rates determined from binary and ternary mixtures could be different,[25] as pointed out by Zollinger.[26]

CONCLUSIONS

Furan is more reactive than thiophene by a factor of 9·3 in the iodine and 11·9 in the tin tetrachloride-catalysed acetylations. These ratios, which confirm the qualitative observations derived from preparative chemical data, represent the first quantitative measurements of the difference in reactivity between these 5-membered heterocyclics in an electrophilic substitution in which a proton is displaced. The difference in reactivity between the two heterocyclic rings is, however, not very large if we consider that the introduction of a Me group in an α-position of the thiophene ring is sufficient to reverse the reactivity order.

Regarding the comparison with benzene derivatives, the present data indicate that the *alpha* position of thiophene is slightly more reactive than the *para* position of anisole. This confirms the previous quantitative observations relative to chlorination,[27] bromination[27] and protodesilylation[10,28] reactions.

The substituent effects in the thiophene ring are those predicted for an electrophilic substitution: a Me group in the α-position increases, and a chloro substituent decreases, the rate of acetylation. Although the substituents examined are too few to test the applicability of a free energy relationship, the data confirm the observation previously made for the bromination reaction,[29] that the mode of transmission and the intensity of the electronic effects in the thiophene and in the benzene rings are similar.

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[25] C. D. Ritchie and H. Win, *J. Org. Chem.* **29**, 3093 (1964).

[26] P. Kreienbühl and H. Zollinger, *Tetrahedron Letters* 1739 (1965).

[27] G. Marino, *Tetrahedron* **21**, 843 (1965).

[28] C. Eaborn, *J. Chem. Soc.* 4858 (1956).

[29] G. Marino, *Atti Acc. Naz. Lincei* **38**, 700 (1965).

TABLE 2. COMPETITIVE EXPERIMENTS OF ACETYLATION

Reactants[*]	Initial Conc of reactants M	Final Conc of products M	Relative rates	Reactants	Initial Conc of reactants M	Final Conc of products M	Relative rates
Furan	1·15	0·160	1	Anisole	1·15	0·0422	1
2-Me-thiophene	1·15	0·244	1·59	Thiophene	1·15	0·106	2·60
Acetic An.(I_2)	1·10			Acetic An.(I_2)	1·11		
Furan	1·72	0·246	1	2-Cl-thiophene	0·487	0·0015	1
2-Me-thiophene	0·688	0·139	1·46	Thiophene	0·461	0·0177	12·7
Acetic An.(I_2)	0·646			Acetic An.(I_2)	0·446		
Furan	0·486	0·0566	1	2-Cl-thiophene	2·71	0·0031	1
2-Me-thiophene	0·892	0·1587	1·60	Anisole	0·667	0·0034	4·52
Acetic An.(I_2)	0·443			Thiophene	0·507	0·0070	12·2
Thiophene	3·18	0·0256	1	Acetic An.(I_2)	0·462		
Furan	0·648	0·0469	9·33	Thiophene	1·33	0·0474	1
Acetic A.(I_2)	0·603			Furan	0·298	0·0944	11·9
Thiophene	2·76	0·0102	1	Acetic An.($SnCl_4$)	0·297		
2-Me-thiophene	0·564	0·0321	15·6	Furan	1·23	0·234	1
Acetic An.(I_2)	0·524			2-Me-thiophene	1·22	0·342	1·56
Thiophene	3·14	0·0330	1	Acetic An.($SnCl_4$)	0·715		
2-Me-thiophene	1·01	0·1533	15·9	Thiophene	3·23	0·0838	1
Acetic An.(I_2)	0·923			2-Me-thiophene	0·973	0·3517	17·2
Thiophene	1·33	0·0066	1	Acetic An.($SnCl_4$)	0·886		
2-Me-thiophene	0·442	0·0382	16·4	Anisole	0·712	0·0566	1
Acetic An.(I_2)	0·432			Thiophene	0·713	0·162	3·10
Thiophene	2·00	0·0053	1	Acetic An.($SnCl_4$)	0·693		
2-Me-thiophene	0·201	0·0097	17·9	2-Cl-thiophene	1·37	0·0814	1
Acetic An.(I_2)	0·188			Thiophene	1·32	0·757	14·0
Thiophene	1·74	0·0033	1	Acetic An.($SnCl_4$)	1·27		
2-Me-thiophene	0·194	0·0065	17·9	Thiophene	1·12	0·0166	1
Acetic An.(I_2)	0·193			Furan	0·375	0·0604	11·8
				2-Me-thiophene	0·412	0·1026	17·3
				Acetic An.($SnCl_4$)	0·366		

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[*] The concentration of the catalyst was always equal to 1/100 of that of the acetic anhydride.

TABLE 3. RETENTION TIMES OF THE ACETYL DERIVATIVES*

Compound	Retention time
2-Acetylfuran	3·0 min
Acetophenone(internal standard)	5·5 min
2-Acetylthiophene	8·6 min
2-Methyl-5-acetylthiophene	13·1 min
2-Chloro-5-acetylthiophene	13·8 min
p-Methoxyacetophenone	37·5 min

* Craig Polyester Succinate, 2 m; 150°, 300 cc H_2/min.

EXPERIMENTAL

Materials. Thiophene (b.p. 83–84°), 2-chlorothiophene (127–128°), anisole (154°) and furan (32°) were pure grade commercial samples, purified by distillation at atm press. 2-Methylthiophene was prepared by a Wolff-Kishner reduction of 2-thiophenaldehyde[30] and distilled, b.p. 112·5°. All the samples used for the competitive experiments were examined by VPC and proved to be at least 99·5% pure.

Ac_2O was refluxed for 5 days with Mg filings[31] and then fractionated through a Todd column using a reflux ratio of 10:1. The medium fraction boiling at 140° was used. Iodine and $SnCl_4$, used as catalysts, were commercial samples of the highest grade of purity available.

1,2-Dichloroethane was dried over $CaSO_4$ and then fractionated. The fraction boiling at 83·5° was used as solvent for the competitive experiments.

A number of ketones was required as standards for the VPC: acetophenone and *p*-methoxyacetophenone (m.p. 38–39°) were commercial samples; 2-acetylthiophene (b.p. 212–214°), 2-acetylfuran (172–173°), 2-chloro-5-acetylthiophene (50–51°) and 2-methyl-5-acetylthiophene(83–85°) were prepared as described in the literature.[16]

Competitive acetylations. Appropriate volumes of stock solns in ethylene dichloride of two or three aromatic compounds and eventually of pure solvent were mixed. To the resulting soln, thermostatted at 25° and well stirred, a soln containing Ac_2O and the catalyst (in the molar ratio 100:1) was added dropwise. The final molar concentrations for each aromatic compound were in the range 0·3–3M; the concentration of the anhydride was kept always smaller than that of every substrate.

The reaction solns were left at 25° for 1–2 days, then poured into a 10% $NaHCO_3$aq. At this point a known amount of an internal standard (acetophenone) was added to the mixture. The mixture was then extracted with ethyl ether; the ether was washed twice with water, dried over Na_2SO_4 and finally distilled off. The residue was analysed by gas chromatography.

Blank experiments were carried out using synthetic mixtures of the various acetyl derivs and the internal standard in order to check how much the molar ratio was altered by the operations (extraction, removal of the solvent, etc.) to which the mixtures were submitted. Corrections were made to take account of these small variations.

Gas chromatographic analyses were accomplished on a Mod. B Erba Fractometer equipped with a thermistor detector. A 2 m by 6 mm stainless steel column packed with Craig Polyester Succinate supported on C-22 Firebrick, was used for all the analytical determinations. The column temp was 150° and the flow rate 300 ml H_2/min.

Under these conditions, a complete resolution of the individual components was achieved; the observed retention times of the examined acetyl derivs are summarized in Table 3.

The amounts of the ketones formed were determined by comparison of the areas of the product peaks with the area of the internal standard peak, using calibration curves made up with synthetic mixtures. The accuracy of the analytical procedure was established from duplicate determinations to be ±2%.

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[30] W. J. King and F. F. Nord, *J. Org. Chem.* **14**, 641 (1949).

[31] A. Weissberger, *Technique of organic chemistry* (2nd Edition) Vol. VII; p. 395. Interscience, New York (1955).

The relative rates were then calculated by means of the equation:[34]

$$\frac{k_A}{k_B} = \frac{\log (A^\circ - X_A)/A^\circ}{\log (B^\circ - X_B)/B^\circ}$$

were A° and B° refer to the initial moles of the competing heterocycles and X_A and X_B refer to the final moles of the corresponding ketones.

Data for individual experiments are summarized in Table 2.

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