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PRIMARY STERIC EFFECTS IN FIVE-MEMBERED HETEROCYCLIC SYSTEMS

ACETYLATION OF ALKYLTHIOPHENES[1]

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Abstract—The relative importance of primary steric effects in acetylation of benzene and thiophene rings was studied. The smaller steric hindrance found in the heteroaromatic system is explained in terms of molecular geometry. A correlation is suggested between the "steric ratio" and bond angles.

RECENT PAPERS of Bak *et al.*[2-4] have pointed out the different molecular geometry of the three fundamental five-membered heteroaromatic compounds: thiophene, furan, and pyrrole. The internal angles of these systems are different, and always smaller than those of benzene.

In connection with our previous studies[5-10] on structure-reactivity relationships in the thiophene ring, we wish to check the influence of molecular geometry on the reactivity of the various positions of thiophene derivatives towards electrophiles.

The factors affecting the isomer distribution in an electrophilic reaction of a mono-substituted thiophene are electronic effects—relative directing power of the sulphur atom and the substituent group—and steric effects, depending essentially on the steric hindrance caused by bulky groups. Further, the importance of the primary steric effects depends on the size of substituents, on the nature of solvated electrophiles, and, finally, on the molecular geometry of substrates.

The difference in angles between thiophene and benzene rings might cause a remarkable difference in the relative importance of the steric effects in these two systems. We wish to report new data making this comparison possible.

From preparative chemistry we can deduce that primary steric effects are somewhat important in varying the directing power of substituents in thiophene derivatives. For example in acetylation of 3-alkylthiophenes[11-13] the percentage of the 2-acetylisomer decreases with the size of the group. Similar results were obtained in formylation.[14]

The use of alkylderivatives is particularly suitable for the clearest separation of the primary steric effects from polar effects because the orienting group can be varied greatly in size without changing its polar character.[15]

In this connection we have studied quantitatively under homogeneous conditions the relative effects of Me and t-Bu groups in an electrophilic substitution of the two systems, in order to obtain a comparison between primary steric effects in benzene and thiophene rings.

It is well known that acetylation is a reaction employed to establish the steric hindrance in benzene derivatives.[16] In such a study Brown and Marino have determined the partial rate factors for AcCl–$AlCl_3$ (1 : 1) acetylation of toluene and t-butylbenzene.

This reaction is not good for heteroaromatic nuclei and we have choosen the $SnCl_4$ catalyzed acetylation by Ac_2O in dichloroethane, already used in our previous study.[6]

RESULTS

The partial rate factors for all the positions of toluene, t-butylbenzene, 2- and 3-methylthiophenes, 2- and 3-t-butylthiophenes have been calculated from isomer distributions and relative rates with respect to the unsubstituted rings.

The isomer distributions, determined by gas chromatographic analysis, are listed in Table 1.

TABLE 1. ISOMER DISTRIBUTIONS IN ACETYLATION BY Ac_2O–$SnCl_4$ IN 1,2-DICHLOROETHANE AT 25°

Compound	*ortho* %	*meta* %	*para* %
Toluene	4·15	0·99	94·86
t-Butylbenzene	~0·0003	2·99	97·01
	3%	4%	5%
2-Methylthiophene	4·15	0·16	95·69
2-t-Butylthiophene	0·06	0·18	99·76
	2%	4%	5%
3-Methylthiophene	74·97	0·47	24·56
3-t-Butylthiophene	14·68	0·04	85·28

The data for acetylation of thiophene derivatives have already been reported from preparative chemistry, but they were not obtained under the same reaction conditions and the isomers were determined only by isolation methods. In fact the methylthiophenes had been acylated by Ac_2O/H_3PO_4,[11] the iso-propylthiophenes by $AcCl/AlCl_3$,[12] the t-butylthiophenes by $AcCl/SnCl_4$,[13] and it is well known that the isomer ratio depends strongly on reaction conditions.[17]

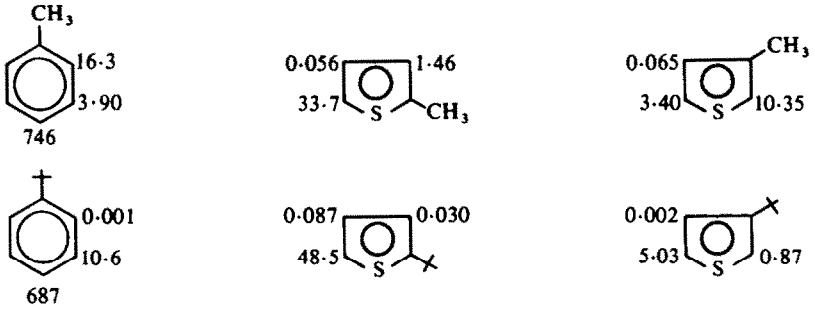
The percentage of *ortho*-t-butylacetophenone is very small. We were able to identify this isomer in the reaction mixture with the aid of an authentic sample, having to vary the detector's sensitivity greatly during the analysis.

The relative rates, obtained from competitive experiments, are quoted in Table 2.

TABLE 2. RELATIVE RATES OF ACETYLATION BY Ac_2O–$SnCl_4$ IN 1,2-DICHLOROETHANE AT 25°

Compound I	Compound II	k_1/k_{11}	Ref
Toluene	Benzene	131	8
Toluene	t-Butylbenzene	1·18	this work
2-Methylthiophene	Thiophene	17·6	6
3-Methylthiophene	Thiophene	6·90	this work
2-t-Butylthiophene	Thiophene	24·3	this work
3-t-Butylthiophene	Thiophene	2·95	this work

Overall relative rates and isomer distributions permit us to calculate the following partial rate factors in relation to the respective unsubstituted ring:



The partial rate factors for the 5-position of the thiophene derivatives, together with the reactivity data for 2-chlorothiophene previously reported,[6] give a satisfactory linear Hammett correlation with a ρ value of $-5{\cdot}7$.

From these data it is also possible to calculate the α/β ratio in acetylation of thiophene derivatives: the ratio $5_f^{3-R}/4_f^{2-R}$ is about 60, both for Me and t-Bu substituents, a value not in good agreement with that reported (200).[8] This discrepancy might be due to a somewhat different sensitivity to the substituent effect between the α and β positions.

DISCUSSION

From data in Table 2 we see that 3-alkylthiophenes are always less reactive than the 2-isomers, although this result is hard to rationalize from pure electronic effects. In fact, using the cited ρ value for $Ac_2O/SnCl_4$ acetylation of thiophene derivatives and supposing the *ortho* activation equal or greater than *para*,[18] the overall reactivity ratio 3-Me/2-Me should be $\gg 1{\cdot}04$.*

Moreover the partial rate factor 5_f for 2-alkylthiophenes should be the same or smaller than 2_f for 3-alkylthiophenes. In fact this is true for reactions with low steric requirements, such as deuterium exchange: Shatenshtein *et al.*[19-20] report, respectively, 340 for 2_f^{3-Me} and 200 for 5_f^{2-Me}. On the contrary our experimental values show that for the acetylation reaction 5_f^{2-Me} is 33·7 and 2_f^{3-Me} is 10·35; for t-Bu derivatives the difference is much larger, going from 48·5 to 0·87. From these results we can deduce the importance of the primary steric effect for this reaction in the thiophene ring.

To measure the steric hindrance to attachment of a reagent, *ortho/para* ratios for alkyl substituents of different size might be considered. Clearly, it is not always easy to evaluate the importance of polar factors in governing these ratios.[21] Moreover the two positions are not equally activated by the various alkyl groups, because of the differences in hyperconjugation and field effects. However, we are interested in comparing the relative *ortho/para* ratios determined for two substituents and not in the values themselves.

In an attempt to compare quantitatively the steric hindrance in benzene and thiophene rings we should consider, for the two systems, the ratio of the *o/p* ratios obtained with Me and t-Bu substituents. This value gives a measure of the degree of steric effects related with the molecular geometry of the substrate, and therefore we call it "steric ratio" (see Table 3). Accordingly, we could take into account o_f and p_f for alkylbenzenes, and 3_f and 5_f for 2-alkylthiophenes, but these positions are not equally activated by the presence of the sulphur atom.

* The predict reactivity ratio was calculated using $\rho = -5{\cdot}7$ and Brown's σ^+, considering $\sigma_o^+ = \sigma_p^+$

For a correct approach to the problem, instead of the *ortho/para* ratios, we were forced to study the *ortho/meta* ratios. In this case, both considered positions of the thiophene ring (3 and 4) are of β type. We have examined also 3-alkylthiophenes, where the concerned positions (2 and 5) are both α, and where the isomer distributions are such to give more accurate results.

Obviously the *ortho* and *meta* positions are not equal from a polar viewpoint, for the above reasons (see for instance the o_f and m_f for $RCOCl/AlCl_3$ acetylation and benzoylation of alkylbenzenes).[16]

However, the *ortho/meta* ratio is also a good measurement of the steric hindrance, since in the electrophilic substitutions of alkylbenzenes the *meta/para* ratio does not depend on the nature of the alkyl group,[21] indicating that the *meta* position is not affected by steric factors. Further, the differences in electronic activation of the *ortho* and *meta* positions are minimized if we consider the ratio of the ratios for the two substituents.

These differences in polar effects can be calculated from Brown's constants and the cited ρ value.* Thus the quantity *o/m* (Me)/*o/m* (t-Bu)—the "steric ratio"—for thiophene derivatives should be about 2.

Our experimental data, calculated from the partial rate factors, are summarized in Table 3.

TABLE 3. STERIC RATIOS IN ACETYLATION OF ALKYLDERIVATIVES OF BENZENE AND THIOPHENE

Compounds	*o/m* (Me)	*o/m* (t-Bu)	$\frac{o/m\ (Me)}{o/m\ (t\text{-}Bu)}$
alkylbenzenes	4·19	$\sim 9{\cdot}4 \times 10^{-5}$	~44500
2-alkylthiophenes	26·0	$3{\cdot}45 \times 10^{-1}$	75·6
3-alkylthiophenes	3·05	$1{\cdot}73 \times 10^{-1}$	17·6

As in the benzene series, the *ortho/meta* ratio for t-butylthiophenes is much smaller than for Me derivatives and thus it is confirmed that the substituent size is affecting the reactivity of neighbouring positions in the heteroaromatic ring also. The importance of the steric hindrance, given by the "steric ratio", is much smaller in thiophene than in benzene system, although the value of the ratio (17·6 or 75·6) cannot be related to the discussed electronic differences (~2).

The different behaviour of the two rings is easily ascribed to the different geometry of the molecules, but, in our opinion, it does not depend only on the situation of their ground states.

Our results do not disagree with the reported observations about the absence of a secondary steric effect in some nucleophilic substitutions of halothiophenes. Although the presence of a Me group reduces about three fold the partial rate factor of an *ortho* position in acetylation, it does not prevent the conjugation of the *ortho* nitro groups in the piperidinodebromination of 2-bromo-3,5-dinitro-4-methylthiophene.[22] In fact, in the latter study the side of the molecule around the Me group remains rigid during the course of the reaction, and therefore it is not affected by changes on the substituted carbon. On the other side, in an electrophilic substitution the steric hindrance of an *ortho* group

* See footnote on page 4669.

varies with the reaction coordinate, since the attacked carbon atom must become tetrahedral in the Wheland complex, giving rise to changes in bond angles.

Obviously the importance of primary steric effect, with the same substituents, depends on the size of electrophile: so in deuteration of 3-t-butylthiophene the main product was 3-t-Bu-2-D-thiophene,[23] because of the low steric requirements of the reaction center in the intermediate.

Further, the importance of the primary steric effect, when the electrophile is bulky enough, might be correlated with the variation in bond angles in passing from the ground state to the Wheland complex. So, in the benzene system the difference is 10·5 degrees; in the thiophene ring, with internal angles of 111·5 and 112·5 degrees respectively,[2] the difference from 109·5 is smaller and therefore the steric hindrance should be less important. This fact might also be the cause of the smaller steric ratio, for 3-alkylthiophenes, which are substituted in an *alpha* position.

This idea is supported by the linearity of a plot of log "steric ratio" *vs* Δ degrees. In order to check this point, work is in progress to extend our study to other heteroaromatic compounds.

Of course, this argument is sound only so long as the transition states for all the positions of the considered systems are very similar. There is much supporting experimental data, but even so the position is not yet completely resolved.

EXPERIMENTAL

Thiophene (b.p. 84°), 2-methylthiophene (b.p. 112·5°), 3-methylthiophene (b.p. 115·5°), toluene (b.p. 110·5°), and t-butylbenzene (b.p. 168°) were pure grade commercial samples purified by distillation. 2- and 3-t-butylthiophenes were prepared according to the method of Wynberg and Viersum,[24] and fractionated through a Todd column (b.p. respectively 163° and 170°). Reagents and solvent were commercial products purified according to literature procedures.

Competitive experiments. These were carried out at 25°, using a molar ratio 1 : 100 of $SnCl_4$ with respect to Ac_2O as described in a previous paper.[6]

Gas chromatographic analysis. To determine the isomer distributions and the reactivity data from competitive experiments, the gas chromatographic analyses were accomplished on a C. Erba Fractometer, mod. GI, equipped with a flame ionisation detector, using stainless steel columns (2 m × 4 mm), packed with Carbowax 20 M 10% or LAC 728 10% on 60–80 mesh Chromosorb W, operated at proper temp.

The isomeric ketones were identified by mass spectra, accomplished, for the courtesy of Dr. Maroni, on a CH7 model GCMS at Varian (Bremen). The standard compound for the analysis of *ortho*-t-butylacetophenone has been prepared according to the literature procedure.[25]

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