A Theoretical Study of the Site Selectivity of Activating Methylthio and Methoxy Groups in the Synthesis of Isoquinolines

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The site selectivity of activating methylthio and methoxy groups in the synthesis of isoquinolines has been studied theoretically in terms of the static index approach. The dependence of the relative amounts of *ortho*- and *para*-isomer produced upon the nature of the electrophilic group has been explained in terms of the degree of charge localization in the electrophile, together with the calculated electronic structure of the activated benzene ring.

Most of the widely used syntheses of isoquinolines proceed *via* acid-catalysed attack of a suitable functionalized *N*-substituted phenethylamine or benzylamine on the benzene ring of the amine. To facilitate the attack of the electrophilic function of the side-chain upon the benzene ring, the latter is activated by suitable electron-donating substituents. In the absence of such activating groups, the reaction either fails, or gives poor yields. The most widely used activating group has been methoxy, but this is difficult to remove after cyclization and is thus to be avoided when the unsubstituted ring is sought. However, methylthio has been found to be a suitable alternative,[1] which may be subsequently removed by reductive desulphurization. With the MeS group placed *meta* to the attacking side-chain, activation of the positions *ortho* and *para* to this group can yield two possible isomeric final products. The reactions we have studied are detailed in the Scheme; the first product is referred to as the *ortho*-isomer and the second as the *para*-isomer. The charged structures depicted in the Scheme are simplistic, taking no account of charge delocalization or solvent participation. However, we believe them to represent the major features of the reactive state. We have found that the relative amounts of the *ortho*- and *para*-products are dependent upon the nature of the side-chain electrophile.[2] A summary of these experimental results, mainly for methylthio activation, together with some for methoxy activation, is given in the Table. (Reaction conditions for the methoxy analogues were as described for the methylthio compounds.[2] The product ratios for reaction C were derived from cyclizations in anhydrous hydrogen fluoride.[2]) It can be seen that the products range from essentially 100% *ortho*-isomer (for a carbocation electrophile), to 100% *para*-isomer (for an iminium ion electrophile). In this paper we seek a theoretical explanation of these findings.

Table. Isomer composition of activating MeS and MeO groups

	MeS			MeO		
	Isomer composition [Yield (%)]			Isomer composition [Yield (%)]		
Reaction	*ortho*	*para*	*ortho*/*para*	*ortho*	*para*	*ortho*/*para*
A	95					
B	74					
C	69	7	10	59	41	1.4
D	49	37	1.3	10	58	0.2
E	40	40	1.0	45	53	0.8
F	8	53	0.2			
G	7	47	0.1	4	71	0.06
H		21			25	
I		58			68	
J		89		7.5	78.5	0.1
K		94		2	85	0.03

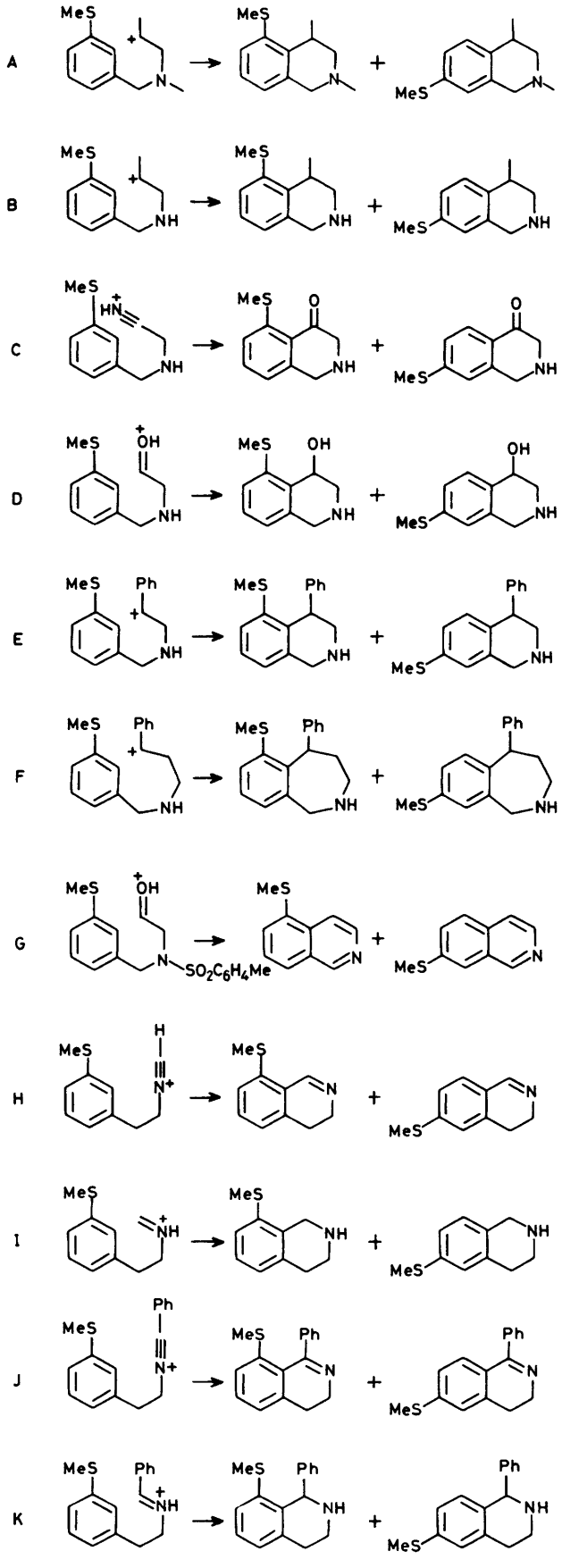
Theoretical Methods

We shall consider electronic and steric effects, both of which may influence the relative amounts of *ortho*- and *para*-isomer produced. The simplest theoretical approach which accounts for electronic effects is to attempt to correlate the observed reactivities with the ground-state elecronic structures of the reactants, using electronic properties ('static indices'), which are taken to be indicative of important factors influencing the transition state.[3,4] Such simple considerations are appropriate in the absence of accurate calculations of the transition state, which are certainly not feasible at the present time if *ab initio* wavefunctions are employed.

We examine the possibilities that the reactions considered may be dominated by 'frontier orbital'[4] or 'charge-control'[3] considerations. Attack on the benzene ring by a 'hard' electrophile, in which the positive charge is localized, would be expected to be 'charge-controlled,' and in that case the preferred site of attack may be expected to correlate with the charge distribution of the methoxy- or methylthio-substituted benzene ring.

In the 'frontier orbital' approach, attention is focused on the HOMO of the nucleophile (the benzene ring) and the LUMO of the electrophile, the stability of the transition state being taken to depend on the amplitudes of these two MOs on the atoms involved in bond formation.[4,5] Such an approach is generally taken to be appropriate for attack by a 'soft' electrophile, in which the positive charge is delocalized.[4]

To examine both the charge distribution and form of the HOMO of the nucleophile, *ab initio* SCF–MO calculations were carried out for 3-methyl(thioanisole) and 3-methylanisole. The geometries of these two molecules were estimated as follows. Data for 3-methylanisole were taken from published electron diffraction results for anisole;[6] a methyl group in a standard geometry[7] was added to the 3-position to take some account of the side-chain of the benzene ring. In both molecules the methyl groups attached to the heteroatom are assumed to be coplanar with the benzene ring. Bond lengths and angles for the PhS fragment of 3-methyl(thioanisole) were taken from those quoted in a microwave study of benzenethiol;[8] the CH_3S group geometry was adapted from that of dimethyl sulphide.[9] As for anisole, a methyl group was added at the 3-position to model the side-chain. Although this side-chain is different for the



Scheme.

various reactions, such differences are not expected to alter the electronic structure of the benzene ring so as to alter significantly the conclusions of this study. The SCF–MO calculations were carried out in an STO-3G basis.[10]

Theoretical Results

The calculated charge distributions obtained by a Mulliken population analysis, and HOMO coefficients are given in the Figure. From these results we conclude that (*a*) a 'charge-controlled' mechanism favours the *ortho*- over the *para*-isomer, since the corresponding formal atomic charges at the *ortho*- and *para*-positions are −0.094 and −0.080 for 3-methyl(thioanisole) and −0.095 and −0.086 for 3-methylanisole; (*b*) a 'frontier orbital' mechanism favours the *para*- over the *ortho*-isomer since the magnitudes of the HOMO coefficients are 0.385 and 0.248 at the *para*- and *ortho*-positions for 3-methyl(thioanisole) and 0.493 and 0.309 for 3-methylanisole. Thus, from these quite simple theoretical considerations we would expect that cyclization involving a 'hard' electrophile would favour the *ortho*-isomer, whilst a 'soft' electrophile would favour the *para*-isomer.

The electrophiles in the Scheme can be divided into three main classes: carbocations, in which the charge resides formally on a carbon atom; protonated carbonyls in which the charge lies on an oxygen atom; and protonated imines and isonitriles in which the charge resides, at least formally, on a nitrogen atom. Electronegativity considerations suggest that the positive charge on the electrophilic carbon atom will be least for the third group, somewhat greater for the second group, and greatest for the carbocations. Taking the degree of positive charge localization to determine the 'hardness' of the electrophile leads to the prediction that the carbocations will give the greatest *ortho*:*para* ratios, the carbonyls rather lower ratios, and the imines and isonitriles the lowest ratios of all. This is the generally observed trend from the data in the Table.

There are however exceptions to these simple rules, evident from the data in the Table, which we now discuss. Groups attached to the reactive carbon atom of the electrophile may exert an influence on the 'hardness'. In particular, a phenyl group will partially delocalize the positive charge, leading to a decrease in 'hardness,' and to a predicted lowering of the *ortho*:*para* ratio. This is indeed found experimentally for the reactions E and F as compared with A and B. However, the reaction F leads to considerably less *ortho*-isomer than does E, in spite of very similar electronic effects. Large groups attached to the electrophilic carbon atom may be expected to favour the *para*-isomer because of steric interactions with the XMe group. The difference observed between E and F may possibly be

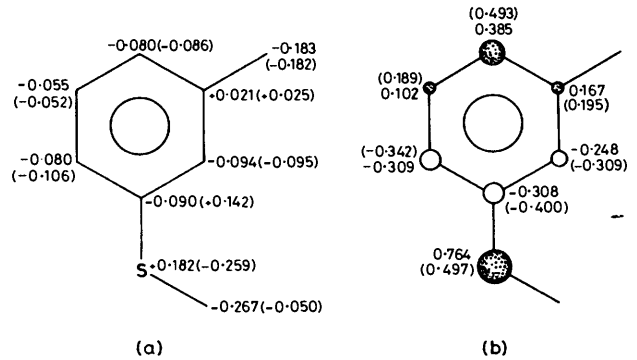


Figure. Electronic structure of 3-methyl(thioanisole) and 3-methylanisole. (a) Formal atomic charges. (b) Coefficients of the HOMO. The values for 3-methylanisole are given in parentheses

attributed to the increased steric repulsion on formation of the seven- as opposed to the six-membered ring on cyclization. However, the observed differences in *ortho*:*para* ratio between D and G cannot be explained by our simple considerations. Furthermore, C unexpectedly appears from the *ortho*:*para* ratios to involve a harder electrophile than the isonitriles.

Turning now to the data available for methoxy, as opposed to methylthio activation (Table), we note that the trends discussed for the latter group are also present here. However, the *ortho*:*para* ratio is in most cases smaller than for the corresponding methylthio-activated reaction. The calculation for 3-methylanisole reveals *smaller* charge differences between the *ortho*- and *para*-positions than for 3-methyl(thioanisole) (Figure). Hence, a 'charge-controlled' mechanism still favours production of the *ortho*-isomer, but not to such an extent as in the methylthio case. This effect is reinforced in the 'frontier orbital' mechanism since in the HOMO of 3-methylanisole (Figure) there is a *larger* difference between the magnitudes of the coefficients at the *ortho*- and *para*-positions than in the case of 3-methyl(thioanisole). Thus, the smaller *ortho*:*para* ratio observed for methoxy activation may be attributed to these two effects.

Conclusions

We have used the static index approach to understand the site selectivity of activating groups in the synthesis of isoquinolines. We find that considerations of the degree of charge delocalization in the electrophile, together with calculations of the electronic structure of the nucleophile, are broadly able to account for the observed trends in the isomer product ratios in these cyclization reactions. However, the role of steric effects in such reactions has yet to be more clearly defined.

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