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A THEORETICAL STUDY OF ELECTROPHILIC SUBSTITUTION ON AMINOPHENOLS AND AMINOBENZENETHIOLS

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Abstract—Some electrophilic substitutions on aminophenols and amibenzenethiols have been studied taking into account the electrostatic perturbation caused by the attacker on the substrate molecule. The predicted reactions agree well with experimental results.

INTRODUCTION

The theoretical study of the reactivity of aminophenols and aminobenzenethiols is of interest as these compounds are important in the fields of biochemistry, medicine, dyes, photography, polymers, etc.

The enormous variety of derivatives of these molecules is due to substitution on the -OH (or -SH) group, the amino group, and different positions on the aromatic ring.

The classical reactivity indexes (electron density, free valence, polarisability, etc) are based on the isolated molecule approximation and therefore they predict only one attacked center, generally one of the ring positions.

Klopman[1] has developed a perturbation method which takes into account the influence of the attacking species on the orientation of the substitution reaction. In a similar way, Chalvet *et al.*[2] developed a unified theoretical treatment of the transition state for reactions of unsaturated molecules ("delocalized model"), where the reagent is represented by just an orbital containing two, one or no electrons, depending on the nucleophilic, radical or electrophilic nature of the attack, respectively.

Yáñez *et al.*[3,4] have recently modified these methods, by introducing the electrostatic perturbation caused by the attacker on the substrate molecule. In this paper, we use these methods to study electrophilic substitutions on aminophenols and aminobenzenethiols. We have also calculated the values of the classical indexes to compare their predictions with our results.

Choice of parameters

For the Hückel type calculations, required by the Klopman's and Chalvet's methods, we have chosen the following parameters[5,6]

$$h_O = 2\cdot0 \qquad k_{C\text{-}OH} = 0\cdot9$$
$$h_N = 1\cdot5 \qquad k_{C\text{-}NH_2} = 0\cdot9$$
$$h_S = 1\cdot0 \qquad k_{C\text{-}SH} = 0\cdot8$$
$$h_C\ (\text{adjacent to N, O or S}) = 0\cdot1.$$

The last parameter has been introduced to take into account the inductive effect of the substituent groups.

The value of h, which characterizes the attacking reagent, varies from $-3\cdot0$ to $3\cdot0\beta$ units.

The atoms in the different isomers of each family are numbered as in Fig 1.

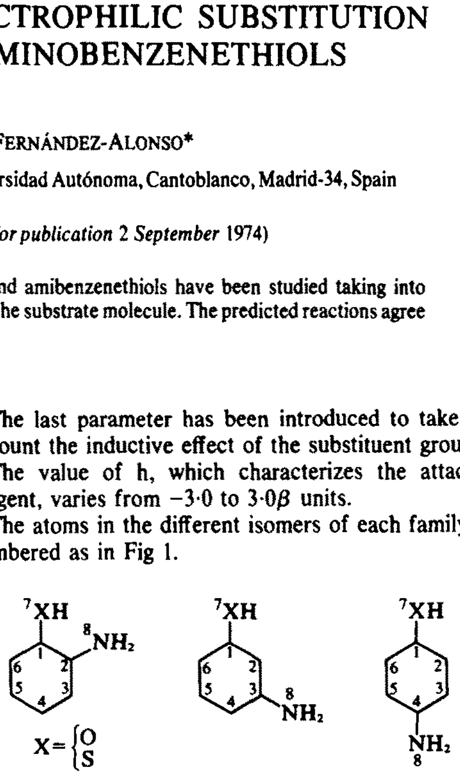

Fig 1. Numbering of Atoms.

RESULTS AND DISCUSSION

Table 1 presents the values of the classical indexes, for electrophilic reactions of aminophenols.

The electron density, free valence, polarisability and superdelocalizability indicate that the *ortho* position relative to the amino group (position 2 in the *m*-aminophenol), is the most reactive in the three isomers. However, the frontier electron density predicts position *para* to the amino group as the most reactive one, for the *o*- and *m*-aminophenol.

Experimentally it has been found that the substitution occurs on either of the two positions depending on the reagent.

The classical indexes for aminobenzenethiols are given in Table 2, and they indicate that the substituents go to position *ortho* relative to the -SH group; however, the frontier electron density predicts substitution on position *para* to the -SH group. But in the literature reviewed we have not found electrophilic substitutions on the ring.

The results of the modified delocalized model (MDM) for the electrophilic reactions of *o*-aminophenol are plotted in Fig 2, where the stabilization energy of position

Table 1. Classical indexes for electrophilic reactions of aminophenols

Isomer	Position	Electron density (q_r)	Free valence index (F_r)	Atomic polarisability (Π_r)	Frontier electron density (δ_r)	Superdelocalizability (S_r)
ortho	3	1·0467	0·4251	0·4117	0·0447	0·9975
	4	1·0241	0·4027	0·4016	0·0965	0·9394
	5	1·0340	0·4067	0·4042	0·1667	0·9936
	6	1·0356	0·4170	0·4067	0·0027	0·9394
meta	2	1·0832	0·4475	0·4185	0·0340	1·1003
	4	1·0719	0·4333	0·4142	0·2121	1·1004
	5	0·9962	0·3943	0·3956	0·0071	0·8296
	6	1·0706	0·4292	0·4118	0·2692	1·0965
para	2	1·0326	0·4175	0·4077	0·0625	0·9740
	3	1·0437	0·4255	0·4128	0·0952	1·0054

Table 2. Classical indexes for electrophilic reactions of aminobenzenethiols

Isomer	Position	Electron density (q_r)	Free valence index (F_r)	Atomic polarisability (Π_r)	Frontier electron density (δ_r)	Superdelocalizability (S_r)
ortho	3	1·0479	0·4247	0·4111	0·0093	1·0002
	4	1·0362	0·4086	0·4064	0·1198	1·0505
	5	1·0334	0·4057	0·4036	0·0707	0·9996
	6	1·0486	0·4283	0·4153	0·0468	1·0540
meta	2	1·0958	0·4585	0·4251	0·0387	1·2037
	4	1·0835	0·4390	0·4172	0·2245	1·2004
	5	0·9961	0·3934	0·4172	0·2245	1·2004
	6	1·0814	0·4396	0·4186	0·1890	1·2033
para	2	1·0438	0·4282	0·4164	0·0843	1·0653
	3	1·0431	0·4246	0·4122	0·0533	1·0115

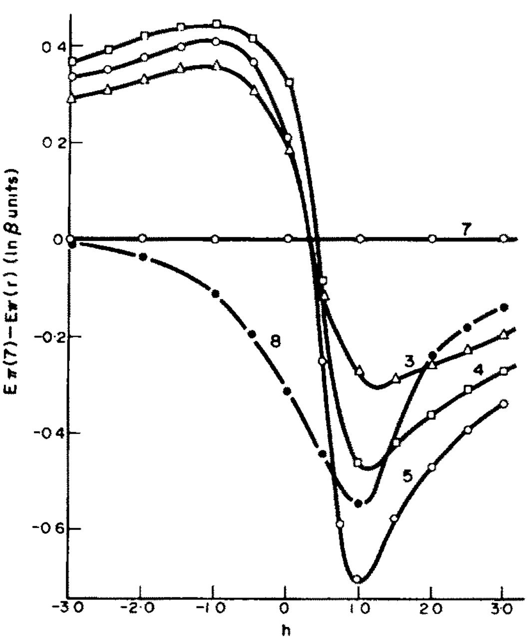

Fig 2. The variation of the relative energies for the electrophilic attack on *o*-aminophenol.

7 (which corresponds to the -OH group) is taken as the level of reference.

It can be observed that for reagents with $h < 0{\cdot}0\beta$ units, substitutions must occur precisely on the groups -OH and $-NH_2$; while, for reagents with $h > 0{\cdot}0\,\beta$ position *para* to the amino group is the most favoured one. This conclusion is verified experimentally by alkylation of *o*-aminophenol occuring on the -OH group,[7] on the amino group[8,9] or on both positions simultaneously, closing an oxazole ring.[10–12]

The triphenylmethyl carbonium ion reacts on position *para* to the amino group,[13,14] in agreement both with the frontier electron density prediction and with our results. However, when the amino and -OH groups are protected, halogenation of the *o*-aminophenol occurs on position 3[15] (*ortho* to the amino group). The MDM indicates position 3 to be the most reactive—not counting the substituents—and it should be the one substituted when these groups are protected (Fig 2).

As we cannot know the value of h which corresponds to each attacking ion, it is not clear whether the different behaviour of the triphenylmethyl carbonium ion and the halogen ion is due to their having very different h values or to steric effects.

The results for the *m*-aminophenol are shown in Fig 3. For reagents with h less than $-2{\cdot}0\,\beta$, less than $0{\cdot}5\,\beta$ or greater than $0{\cdot}5\,\beta$ the most favoured positions are the

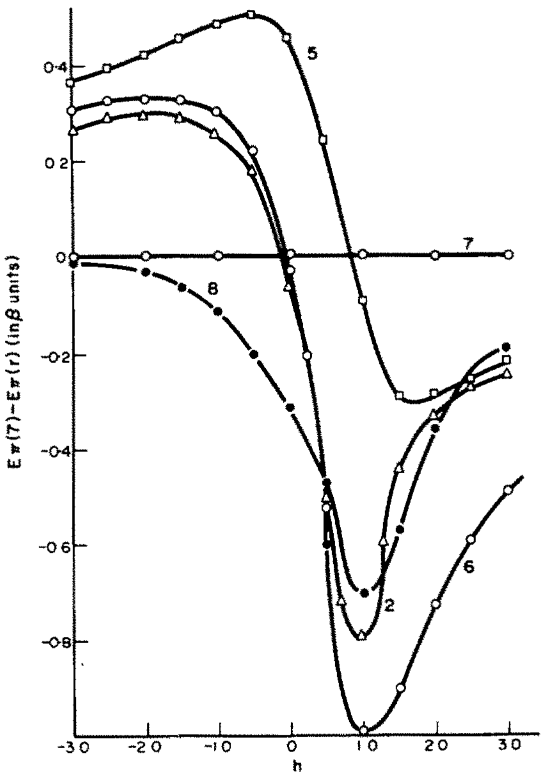

Fig 3. The variation of the relative energies for the electrophilic attack on *m*-aminophenol.

-NH_2 and -OH groups (the -NH_2 is never less reactive than -OH), the amino group, and position 6 (*para* to the -NH_2), respectively.

Experimentally it is found that alkylation reactions occur on the amino group,[16] on the -OH group[7,17] and on both groups simultaneously. Contrary to our results some substitutions occur only on the -OH group. Tritylation and carboxylation take place at position 6.[13,18,19] Sulphonation and nitration occur at position 2[20,21] (*ortho* to the amino group) which is the most reactive one (Fig 3) when taking into account that these substitutions cannot take place on the -NH_2 or -OH groups.

Figure 4 shows our results for *p*-aminophenol, indicating that substitutions must occur at positions 7 and 8, for reagents with $h < 0{\cdot}0\ \beta$, in agreement with the experimental results for alkylation;[7,23-25] but when $h > 0{\cdot}0\ \beta$ substitutions will occur at position *ortho* to the amino group. In fact, chlorination and bromination of *p*-aminophenol yield 3,5 - dichloro - *p* - aminophenol and 3,5 - dibromo - *p* - aminophenol, respectively.[26,27] Halogenation of *p*-aminophenol occurs for values of h greater than $0{\cdot}0\ \beta$, while for *o*-aminophenol h is smaller than $0{\cdot}25\ \beta$. A similar fact was also noticed by Decoret *et al.*[28] in the bromination of furan, pyrrole, thiophen and some derivatives where $-0{\cdot}9 < h \simeq 0{\cdot}15$. In the present case the differences observed in h are a direct result of the form of the Huckel

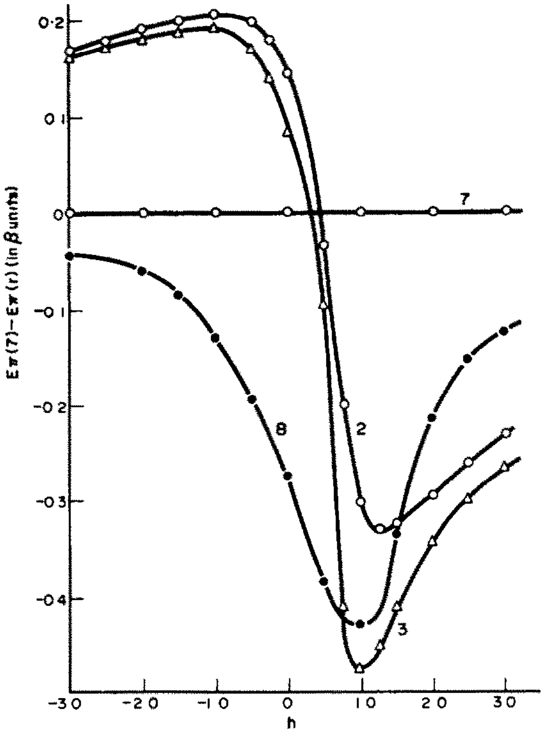

Fig 4. The variation of the relative energies for the electrophilic attack on *p*-aminophenol.

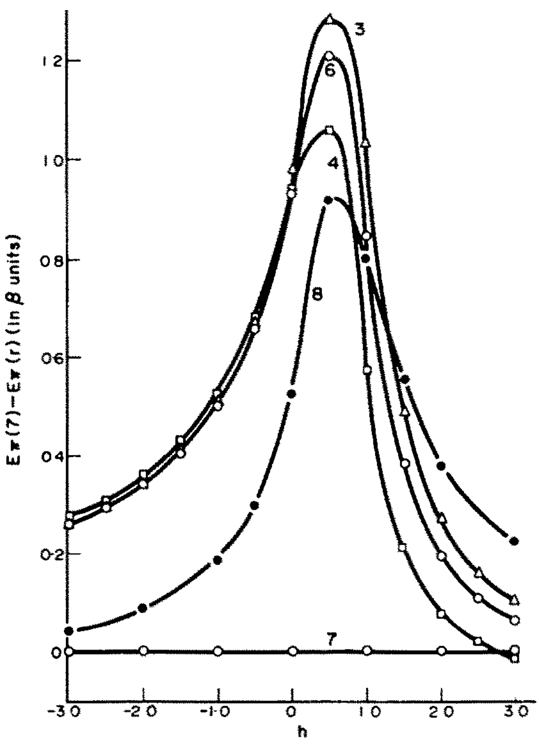

Fig 5. The variation of the relative energies for the electrophilic attack on *o*-aminobenzenethiol.

matrix for the two isomers, and they can be explained by the influence of the substrate on the attacking reagent.

p-Aminophenol, in opposition to the *ortho*- and *meta*-isomers, does not react at all with the triphenylmethyl carbonium ion;[13] this cannot be totally explained by the stabilization energies for the *p*-aminophenol reactions being smaller than those for the other isomers, since other substitutions do take place, and it is probably due to steric effects.

Our results for *o*-, *m*- and *p*-aminobenzenethiol are given in Figs 5, 6 and 7, respectively. The predicted behaviour of these compounds is completely different from that observed for aminophenols, since positions 7 and 8 (the -SH and $-NH_2$ groups, respectively) are always the most reactive for all the attackers studied. The experimental results we have found in the literature show that substitutions occur on the -SH group[29-31] and only on the $-NH_2$ group when the former is protected.[32] In the *o*-amino-benzenethiol substitutions occur some times on both groups simultaneously, closing a thiazole ring[33-35] and tritylation occurs always at position 7 (-SH group).[14]

When the predictions from the frontier electron density and those coming from the other indexes are different, it can be observed that the MDM usually indicates a crossing of the curves representing the stabilization energies for the two positions involved. That is:

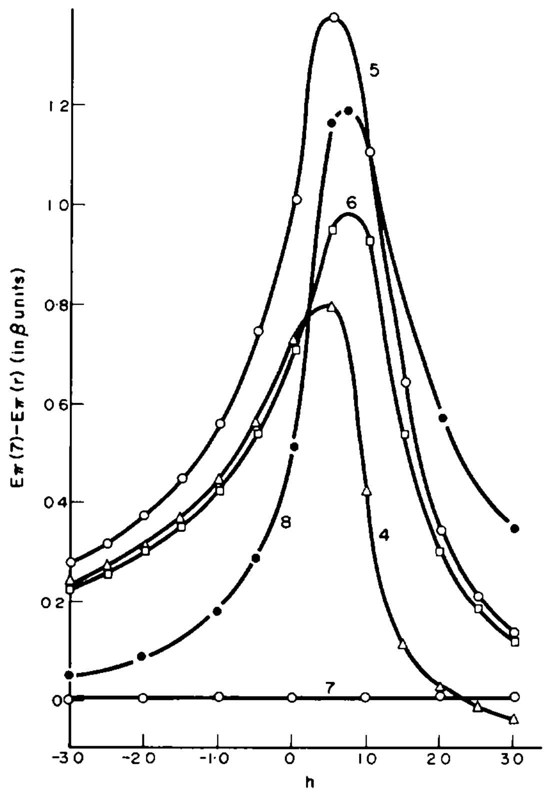

Fig 6. The variation of the relative energies for the electrophilic attack on *m*-aminobenzenethiol.

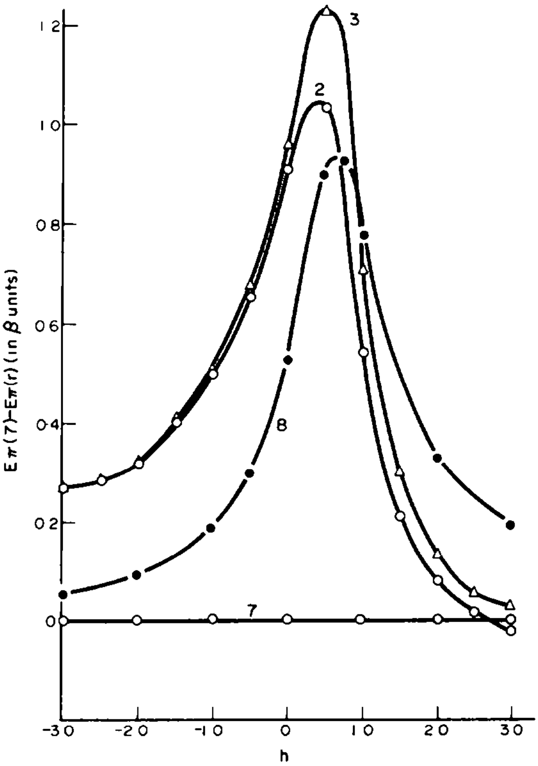

Fig 7. The variation of the relative energies for the electrophilic attack on *p*-aminobenzenethiol.

substitution occurs on either position according to the characteristics of the reagent. This is confirmed by the fact that those curves do not cross for *p*-aminophenol and *p*-aminobenzenethiol, and in these cases the predictions from electron density and frontier electron density agree.

We can conclude that the MDM predictions for electrophilic substitutions on aminophenols and amino-benzenethiols are in good agreement with experimental results, without having to propose special mechanisms for the tritylation reactions.[36]

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