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ON THE APPLICABILITY OF THE MNDO METHOD TO STUDIES OF NUCLEOPHILIC AROMATIC SUBSTITUTION IN POLYFLUOROAROMATICS

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SUMMARY

Calculations have been carried out for several monocarbocyclic highly fluorinated systems: where hydrogen bonding is unlikely to be a problem, the theory correctly orders the isomeric intermediates but the energy differences are not great enough. Calculations with a gegenion in one case improved matters, but did not overcome this difficulty. Preliminary attempts to study the reaction pathway show promise for CHF only systems, but chlorine-containing species are ill behaved. It is concluded that the method shows some promise in this field.

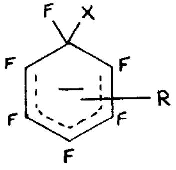
INTRODUCTION

In these laboratories there has been a continuing interest in nucleophilic aromatic substitution. In particularly this focuses on the reactions of polyfluorinated materials [1] and occasionally less heavily halogenated species [2]. Consequently there is an evident interest [3, 4, 5] in deciding which of several possible positions would be first attacked; in particular, a theoretical method which showed a successful pedigree in known cases and which was not too expensive in computer time, would have obvious attractions, particularly in view of the recent breakdown [6] of the 'modified 1π' theory for the case of perfluoroanthracene.

Studies have been undertaken of the usefulness in this regard of the now well established MNDO [7] method, and this report records the initial results.

Two kinds of study are reported: firstly, a number of orientational studies, to see whether the energy differences calculated, for different orientations of attack, fit the observed isomer distributions and hence rates of formation; secondly, studies of the reaction pathway have been undertaken to see if any new insights might be gained, e.g. into the reasons why F^- is usually lost before Cl^-. Both studies were made using the standard program [8] mounted on a CDC 7600 computer at the University of Manchester Regional Computer Centre.

In the first study, calculations have been performed for anions of type (1), and the heats of formation predicted.



$X = H, F, NH_2, NH_3, OH$
$R = H, OH, NH_2$

With some exceptions, detailed below, the geometries were fully optimised, and the results are set forth in Table 1. These calculations correspond to the rather hypothetical 'gas phase' situation, wherein the nucleophile approaches the position of attack and forms the Wheland (Meisenheimer) intermediate and it is then assumed that the energy differences between these intermediates reflect the differences between the relevant transition states. This approach is close to the traditional ones where the results e.g. of the interaction of β-fluorine with the anionic charge [4], or of the 1π effect [3] on the stabilities of the various possible isomeric Wheland intermediates are considered. This approach is plainly open to some criticism, since solvent effects are known [9] to be of importance in some cases of simple nucleophilic attack, and since no account is taken of gegenions, either with or without their solvent sheaths.

DISCUSSION

The results in the table are rather mixed- thus pentafluorobenzene actually gives, in all the reported cases, substantially more para substitution than the other two positions put together; Brook, Burdon and Tatlow [10] report for two cases more than 90% para product. The

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Attempts to calculate e.g. $X=F$, $R=NO_2$ gave difficulties with non-convergent SCF, and have been temporarily abandoned.

calculations clearly do not reproduce this, albeit two sets do predict para to be the predominant position of attack. The results for attack by NH_2^- seem wholly wrong, however.

The predictions for substitution in pentafluoroaniline are again varied; here, calculations for the 'simple' nucleophiles H^- and F^- correctly [11] predict preponderant meta substitution; here the experimental results suggest about 80% meta product is correct. Anomalously, in the case of reaction of concentrated aqueous ammonia with pentafluoroaniline in a sealed tube, the literature reports no ortho product at all.* It does seem, that the calculated slight preference for ortho over para attack does not follow experiment.

Calculations using amine nucleophiles, however, do not fit the experiments: thus, attack by NH_2^- is predicted to give mostly ortho, and attack by NH_3 is predicted to give ortho and meta attack, with only minor para attack. The predicted high ortho rates apparently arise via hydrogen bonding, which is not possible for the other isomers.

To check that it really is hydrogen bonding which favours ortho attack in this case, a series of calculations were made using OH^- as nucleophile: here the HOC plane was kept perpendicular to the ring plane so that in these calculations hydrogen bonding to the ortho position was prevented. Here the calculation favours meta attack, but the experimental preference for para over ortho substitution in the minor products is not reproduced. Logically, this sequence indicates that solvation of the ring substituent and/or the incoming nucleophile, both before and after bond making, must have important effects, since intramolecular hydrogen bonding will thus be disfavoured, and the steric effects would also reduce ortho attack.

In a final series of this type, attack by NH_2^- on pentafluoroanisole, here represented by pentafluorophenol since the loss of the OH proton is not a worry in the calculation, has been performed. The calculation does not reproduce the experimental data [12] well. Again, ortho attack is favoured more by the calculation than by experiment and it may be that hydrogen bonding, which is difficult to remove from the calculation in this case, is important here. More worryingly, the preference for para

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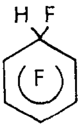
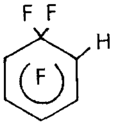
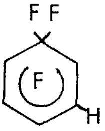
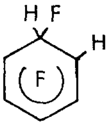
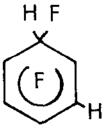
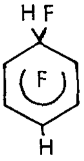
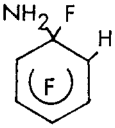
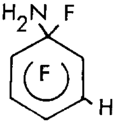
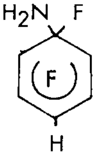
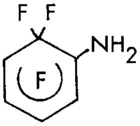
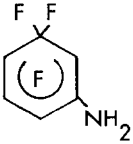
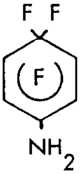
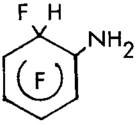
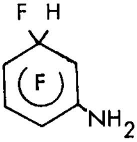
*It is possible that this is an experimental artefact of the analytical method employed which depends upon cyclisation to the benzimidazole which mighteasily be lost if present in small amounts; thus some low value (say 2-3%) of ortho substitution is possible here.

TABLE 1

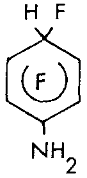
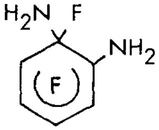
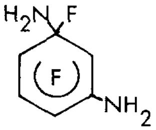
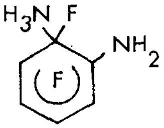
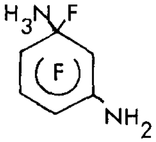
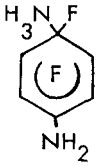
Heats of formation calculated for various species using MNDO

Structure of anion	Heat of formation kcal/mole	ΔH_f	Relative rate at 25°C	Predicted % of product
	-303.9279			
	-304.2744	.63	.345	30.4
	-304.1936	.71	.291	25.6
	-304.9032	0.0	1	44.0
	-253.1560	.78	.268	25.9
	-253.1577	.78	.268	25.9
	-253.9380	0.0	1	48.2

Structure of anion	Heat of formation kcal/mole	ΔH_f	Relative rate at 25°C	Predicted % of product
	-249.2792	.026	.957	51.7
	-248.7548	.550	.395	21.3
	-249.3052	0.0	1	27.0
	-300.8780	1.647	.061	5.5
	-302.5250	0.0	1.0	90.1
	-301.1412	1.385	.097	4.3
	-250.3179	1.2992	.112	9.5
	-251.6171	0.0	1.0	84.5

(Continued overleaf)

TABLE 1 *(cont)*.

Structure of anion	Heat of formation kcal/mole	ΔH_f	Relative rate at 25°C	Predicted % of product
	-250.4549	1.1622	.141	6.0
	-249.0734	0.0	1.0	96.6
	-247.0261	2.047	.0315	3.0
	-245.7271	3.346	.0035	0.3
	-207.9709	.0615	.90	40.8
	-208.0324		1.0	45.2
	-207.7421		.61	13.8

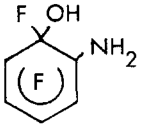
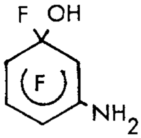
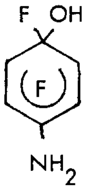
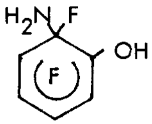
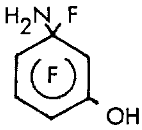
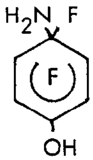
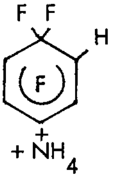
Structure of anion	Heat of formation kcal/mole	ΔH_f	Relative rate at 25°C	Predicted % of product
	-296.9969	1.5042	.0788	6.8
	-298.5011	0.0	1.0	86.7
	-297.3716	1.1295	.1485	6.4
	-297.8797	0	1.0	50.4
	-297.5812	.299	.604	30.5
	-297.7137	.166	.7555	19
	-208.36595	.799	.475	41.1

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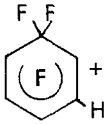
TABLE 1 *(cont).*

Structure of anion	Heat of formation kcal/mole	ΔH_f	Relative rate at 25°C	Predicted % of product
 + $\overset{+}{N}H_4$	-208.36595	1.018	.18	15.6
 + $\overset{+}{N}H_4$	-209.16575		1.0	43.2

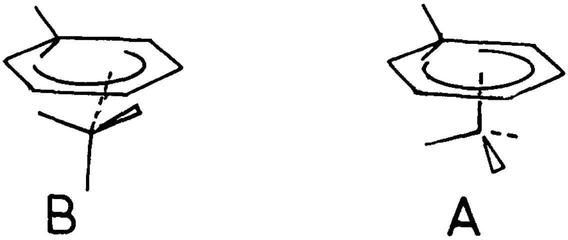


Fig. 1 Trial geometries for the gegenion calculation

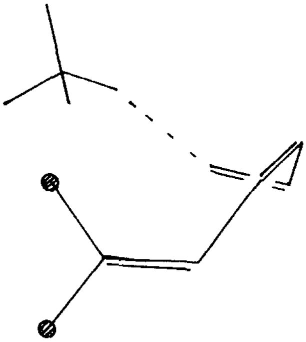


Fig. 2 Converged gegenion geometry - type A

over meta attack (about 2:1) is reversed in the calculations: although para is (slightly) preferred energetically, the statistical advantage of the meta position prevails.

An obvious next step is to consider inclusion of a gegenion in the calculation. For obvious reasons, use of H^+ is not sensible, and no MNDO parameters are yet available for metals, so NH_4^+ was tried. Two initial geometries have been tried (Figure 1), with a single hydrogen atom pointing at the centre of the ring (A), and (B) with it pointing directly away. In both cases the $\overset{+}{N}$-H bond-lengths were all constrained to be equal, thus not permitting decomposition:-

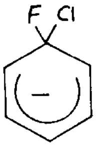
$$\overset{+}{N}H_4 + FAr^- \rightarrow NH_3 + FArH$$

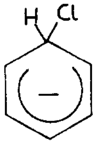
In the former case (using R=H, X=F) the ion pairs converged into the geometry shown in Figure 2, where the inward-pointing H apparently hydrogen bonds to C_6 (rC-H = 1.7A) and the ring has opened out into a hexatriene. This occurred whether or not the ring was constrained to remain planar.

The other trial geometry, with the outward pointing H constrained to remain so, with that $\overset{+}{N}$-H bond held perpendicular to the ring plane, gave a more realistic set of geometries, as shown in Figure 3, which gives a plan view of the converged geometry for the 4-H ion pair. The energies for these three ion pairs are those shown in the table: this approach gives a better result than the initial calculation, the meta percentage being reduced, but it still does not reproduce correctly the high para percentages.

Studies investigating the reaction pathway, have overall not proved very successful. The method used was to obtain a converged geometry for the Wheland intermediate, and then separately to systematically lengthen the C-nucleophile bond and C-F bonds. This was done for lightly fluorinated species, to permit comparison with earlier ab initio studies [2]. It was also intended to look at different leaving groups, initially Cl^-, since it is not well understood by F^- is preferentially lost in most cases.

This latter series of studies foundered, however, since the calculations uniformly predict that Cl^- is an excellent leaving group, so much so that were not recognisable local minima at all, and II showed odd behaviour as one of the C-Cl bonds was systematically lengthened.





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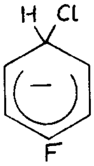

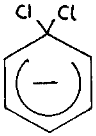

II

In the case of I, as the C-H bondlength changes from 3.0 to 1.1A, the calculated C-Cl distance varies between 4.36 and 3.86A, which is unreasonable. This, together with other data obtained here in similar systems, argues that the stability of Cl^- calculated with these parameters is not chemically realistic.

Confining attention to the very simple system wherein H^- attacks fluorobenzene, it is clear (Figure 4) that: for this model a substantial activation energy is expected (it is hard to estimate this properly, since molecular orbital methods do not correctly reproduce dissociative behaviour [13]); that the Wheland intermediate is a real minimum; and that fluoride ion is lost much ($\sim$35 kcal/mole) more easily than is hydride, all of which accords with expectation.

The large energy difference predicted between the transition state (highest energy point on the curve) and the stable intermediate is, however, disturbing since it goes against the assumption underlying all these simple approaches - that the transition state is close to the Wheland intermediate.

In these calculations, the slight depression in the energy as F^- leaves is due to hydrogen bonding to the *ipso* H as this moves down into the ring-plane.

The final point to note is that bond making is clearly predicted to be rate determining here: this may of course alter in more heavily fluorinated systems.

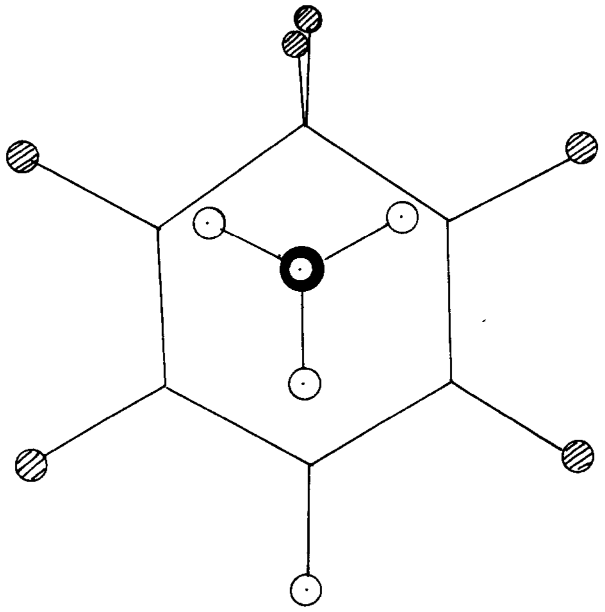

Fig. 3 Converged gegenion geometry - type B

In conclusion, MNDO seems likely to be useful in predicting preferred positions of attack; but with the simple models used here, omitting solvent effects and any entropic considerations due to changes in solvent structure, does not deal well with potentially hydrogen bonding situations. This is probably due mainly to the real hydrogen bonding effects of common solvents and their pre-emptive effects on intermediate structure.

The actual calculated ratios of products are not satisfactory since the energy differences calculated are ususally too small to fit with experiment. [This is, however, an extremely severe test of any quantitative theory in this area, and is not necessarily disqualifying e.g. in the original papers of Dewar errors in heats of formation calculated for the molecules used to calibrate the method scatter up to several kcal/mole]. The best results came in examples where there are marked differences in electronegativity between carbon and the orienting substituent, the results for pentafluorobenzene being rather disappointing. Probably this is due to the non explicit handling of π systems implicit in the MNDO theory.

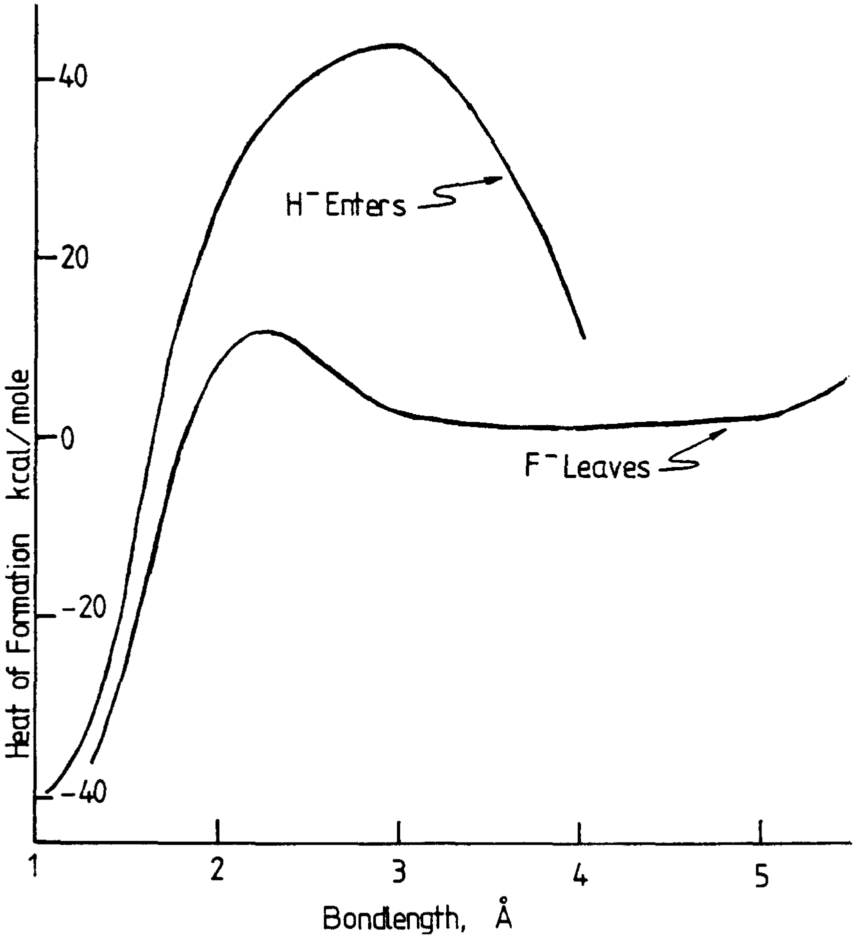

Fig. 4 Heat of formation versus C-F and C-H bondlengths as reaction coordinates

The method is likely to be useful in studies of reaction pathways, but care is needed since some of the disposable parameters are suspect for chlorine, and this may not be unique.

A later report will detail the extension of this study to heterocycles and to polycyclicfluorocarbons.

ACKNOWLEDGEMENT

The author thanks the University of Birmingham for computer time.

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