ALL-VALENCE-ELECTRON SCF–MO CALCULATIONS ON THE ELECTRONIC STRUCTURE AND REACTIVITIES OF SOME HALOGENATED BENZENE AND AZABENZENE DERIVATIVES

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SUMMARY

All-valence-electron CNDO/2 SCF–MO calculations have been performed on some fluoro, chloro and methoxy derivatives of benzene, pyridine and the diazines. The computed charge distributions and the dipole moments are discussed and compared with available experimental data. The relative basicities of the derivatives of pyridine and the diazines have been investigated and an attempt made to correlate the results with known pK_a values. Localisation energies for the nucleophilic substitution of halogen by methoxide ion have also been calculated and the predicted relative reactivities compared with experimental observations, where these were available.

INTRODUCTION

The preparation and reactions of the halogen derivatives of benzene, pyridine and the three diazines, (pyridazine, pyrimidine and pyrazine), have been the subject of extensive experimental work in recent years[1]. Rationalisation of relative reactivities and orientation of substitution in these compounds have generally however been at a qualitative level[2]. For monohalo derivatives in particular, however, attempts have been made to quantify the results in terms of simple molecular-orbital calculations within the Hückel formalism[3]. These calculations have however usually only included the π electrons and have tended to ignore the σ-electron framework. We describe here the results of semi-empirical all-valence-electron SCF–MO calculations on the electronic structures and reactivities of perhalogeno benzene, pyridine and the diazines and some derivatives thereof. The complexity of the systems of interest in respect of this work dictates the use of a reliable computationally inexpensive treatment. We have therefore carried out calculations within the CNDO/2 formalism[4].

THEORETICAL INTRODUCTION

In general, since we are only seeking to rationalise (and predict) trends in electronic structures and reactivities, some of the simplifying approximations which are necessary to carry out any sort of theoretical analysis are not quite as severe as might otherwise have been the case. No attempt has been made to specifically reparametrise the all-valence-electron CNDO/2 SCF–MO treatment and both the one-electron and two-electron integrals were evaluated according to the original formulation of Pople and Segal[4]. Standard geometries have been used as follows. For derivatives of benzene, pyridine and the diazines, the carbon skeleton in each case was taken to be that of the perhydro species either as determined directly from experiment or from standard tables of bond lengths[5]. The requisite bond lengths for the fluoro, chloro and protonated derivatives were taken as 1.33 Å, 1.70 Å and 1.0 Å for C–F, C–Cl and N–H bonds, respectively. In the discussion of Wheland intermediates, the ring geometries were assumed to be unchanged, with the angle at carbon subtended by the halogen and methoxy group at the site of substitution being taken as 109.47° with the plane bisecting the internal angle. The following sections present discussion of the results of computations of (i) charge distributions and dipole moments; (ii) basicities; and (iii) nucleophilic substitution by the methoxide ion.

The calculations were carried out on the Northumbrian Universities Multiple Access Computer (NUMAC) IBM 360/67. Typical cpu times for a convergence limit of 10^{-6} a.u. in energy were *ca.* 6 min for 2,4-dimethoxytrifluoropyridine (58 orbitals) and *ca.* 10 min for perchloropyridine including 3d orbitals on chlorine (69 orbitals total).

RESULTS AND DISCUSSION

Charge distributions and dipole moments

The molecules studied in this work are listed in Table 1 together with computed dipole moments and for comparison experimental values where these are known[6,7]. For such an extensive series of compounds, the listing of individual σ and π charges would be prohibitive in terms of space* and we content ourselves here with a few general comments on trends within series. Some more detailed discussion with respect to electronic redistribution consequent upon protonation for the nitrogen bases considered in this work will be reserved for the next section.

The most significant feature as far as electron distribution is concerned in the pyridine, pyrazine, pyrimidine and pyrazine ring systems is the computed overall negative charge for the nitrogen atoms. This arises largely from σ-electron drift from atoms *ortho* to the nitrogen and π-electron drift from both *ortho* and

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* These have been fully documented elsewhere; see ref. 1.

para atoms. In going from the perhydro to the perfluoro derivatives, the σ-electron drift to nitrogen is drastically reduced; however, in compensation, the π-electron drift is greatly increased, so that overall the total charge at nitrogen remains fairly constant. This has important ramifications as far as discussing the relative ease of protonation of these species is concerned (particularly in terms of an isolated molecule approach, see next section). The net effect of replacing a hydrogen attached to carbon by halogen is to decrease the total electron population on carbon largely as a result of σ-electron drift from carbon to halogen.

TABLE 1

DIPOLE MOMENTS (IN DEBYES) FOR SOME FLUORO, CHLORO AND METHOXY DERIVATIVES
OF BENZENE, PYRIDINE, PYRIDAZINE, PYRIMIDINE AND PYRAZINE

	Experimental values[6, 7]	μ_Q	$\mu_{hyb.}$	μ_{total}
Benzene				
monofluoro-	1.60	1.29	0.32	1.61
monochloro-	1.73	1.80	0.96	2.75
monomethoxy-	1.36	0.60	1.09	1.66
Perfluorobenzene	—	0	0	0
monomethoxy-	—	1.48	0.87	1.91
Pyridine	2.20	0.74	1.58	2.32
2-fluoro-	——	1.94	1.66	3.53
3-fluoro-	—	1.26	1.08	2.01
4-fluoro-	—	0.95	1.38	0.43
2-chloro-	3.25, 3.22	2.27	0.88	3.09
3-chloro-	2.02	1.56	2.35	2.98
4-chloro-	0.78	0.93	0.73	1.66
2K-methoxy- ⎱	1.15	0.61	1.46	2.02
2A-methoxy- ⎰		1.17	2.64	3.81
3K-methoxy- ⎱	2.75	0.28	0.60	0.35
3A-methoxy- ⎰		0.92	2.38	3.28
4K-methoxy-	3.00	0.60	1.44	1.93
Perfluoropyridine	—	0.01	1.09	1.08
2K-methoxy-	——	1.65	0.96	0.86
2A-methoxy-	——	1.47	1.99	2.61
3K-methoxy-	—	1.43	0.26	1.56
3A-methoxy-	—	1.41	1.81	2.93
4K-methoxy-	—	1.55	1.13	2.67
Perchloropyridine	—	0.29	0.76	1.05
Pyridazine	4.32, 3.97	1.21	2.86	4.07
Perfluoropyridazine	—	1.00	2.29	1.29
3K-methoxy-	—	2.33	1.54	1.05
3A-methoxy-	——	1.21	3.20	2.98
4K-methoxy-	———	1.49	1.70	2.24
4A-methoxy-	—	0.73	2.58	3.27

TABLE 1 *(continued)*

	Experimental values[6, 7]	μ_Q	μhyb.	μtotal
3K,4K-dimethoxy-	—	2.67	0.80	2.75
3K,5K-dimethoxy-	—	1.36	1.78	2.24
3K,6K-dimethoxy-	—	1.29	2.40	1.12
4K,5K-dimethoxy-	—	1.50	2.35	3.77
4K,6K-dimethoxy-	—	0.34	2.69	2.82
Pyrimidine	2.0, 2.42	0.67	1.66	2.33
Perfluoropyrimidine	—	0.47	1.13	0.66
2K-methoxy-	—	2.01	1.71	1.63
4K-methoxy-	—	1.71	0.29	1.73
4A-methoxy-	—	1.11	1.85	2.63
5K-methoxy-	—	1.02	1.21	2.22
2K,4K-dimethoxy-	—	2.05	0.95	1.26
2K,5K-dimethoxy-	—	0.79	1.20	0.43
4K,5K-dimethoxy-	—	2.23	0.99	3.21
4K,6K-dimethoxy-	—	1.15	1.05	2.32
Pyrazine	0	0	0	0
2-fluoro-	—	1.34	0.26	1.59
2K-methoxy-	—	0.62	1.09	1.71
24-methoxy-	—	0.74	0.99	1.72
Perfluoropyrazine	—	0	0	0
2K-methoxy-	—	1.57	0.87	1.87
2A-methoxy-	—	1.46	0.96	1.93
2K,3A-dimethoxy-	—	1.49	1.38	0.11
2A,5A-dimethoxy-	—	0.19	0.12	0.07
2A,6K-dimethoxy-	—	0.24	1.87	2.02

For some of the methoxy-substituted compounds, there appears to be a through-space interaction and hence conformational preference for the OCH$_3$ group, and this is illustrated for the case of the monomethoxy derivative of pyrazine and perfluoropyrazine in Table 2.

TABLE 2

CHARGE DISTRIBUTIONS FOR VARIOUS CONFORMERS OF MONOMETHOXYPYRAZINE AND MONO-METHOXYTRIFLUOROPYRAZINE

	Monomethoxypyrazine		Monomethoxytrifluoropyrazine	
	2K	2A	2K	2A
O	−0.221	−0.217	−0.199	−0.199
C	0.131	0.127	0.130	0.096
H$_1$	−0.007	−0.006	0.000	0.001
H$_2$	−0.007	−0.004	0.001	−0.003
H$_3$	−0.005	−0.007	−0.001	0.041

The calculations for the methoxy group were carried out for two principal orientations of the methoxy group, K and A, illustrated below:
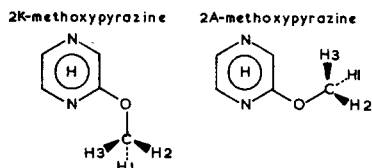

Fig. 1. Position of atoms in 2-methoxypyrazine for the two principal positions of the methoxy group. All the atoms, including those not show, are assumed to be in one plane except for H_1, H_2 and H_3.

The methyl hydrogen, H_3, in the 2A-methoxytrifluoropyrazine bears a noticeable positive charge (0.041) and this feature is also evident for other methoxy-substituted perfluoro compounds with similar orientations. The effect on H_3 can be explained in terms of a through-space interaction with the fluorine atom attached to the adjacent ring carbon. The partitioned bond-overlap populations ($\Sigma P_{\mu i} S_{\mu i}$), (roughly the electron density in the orbital overlap region between nuclei, hence proportional to bond order)[8,9] were also found to be greater for the A orientation. This accords with the lower calculated electronic energy for the A orientation compared to the K orientation. However the nuclear repulsion energy is larger for the 2A-methoxypyrazine making the total energy larger for the 2K-methoxy compounds. (See Table 3).

TABLE 3

INTERATOMIC DISTANCES, PARTITIONED BOND-OVERLAP POPULATIONS AND ENERGY DIFFERENCES FOR THE MONOMETHOXYPYRAZINES

O^a			Perhydro		Perfluoro
2K $\}$	Interatomic distance[b]	N_1	2.123030	N_1	2.123030
2A $\}$	from methyl H_3 to:	H_3	1.502045	F_3	1.441931
2K $\}$	$\Sigma P_{\mu i} S_{\mu i}$		$\{$ 0.0050		$\{$ 0.0047
2A $\}$			$\{$ 0.0122		$\{$ 0.0240
Energy differences[b], 2A-methoxy — 2K-methoxy:					
	Δ(Nuclear repulsion)		942		11 807
	Δ(Electronic)		—907		—11 734
	Δ(Total)		35		73

[a] O is the position and orientation of the methoxy group.
[b] Distances in Å, energies in kJ mol^{-1}.

The dipole moments are calculated as the sum of two components, μ_Q and $\mu_{hyb.}$, from the values obtained from the charge-density matrix, as follows. The

term μ_Q arises from the charge distribution within the molecule and may be calculated from the expression

$$\mu_Q = 2.5416 \sum_A \Delta P_{AA} R_A \text{ debyes} \tag{1}$$

where ΔP_{AA} is the net atomic charge on atom A and R_A is the position vector.

The term $\mu_{hyb.}$ is an atomic polarisation moment due to the hybridisation of s and p and p and d orbitals on a given atom and may be calculated from the off-diagonal elements of the charge-density matrix.

The results of the calculations are given in Table 1 and, although not many experimental results were available, it is evident that there is good overall agreement, in the case of the perhydro and perfluoro derivatives, between μ_{total} and the experimental results. When the components μ_Q and $\mu_{hyb.}$ are considered, it is seen that for pyridine, the diazines and their fluoro derivatives $\mu_{hyb.}$ is of greater importance than μ_Q. In these compounds the values of $\mu_{hyb.}$ is largely dependent on the contribution of the "lone pair" of the nitrogen, and in the case of perfluoropyridine it would appear that the total dipole arises almost entirely from this contribution. Since $\mu_{hyb.}$ is greater in the perhydro series than in the perfluoro series, it may be argued that the centre of charge in the hybrid orbital of the "lone pair" must be displaced further from the nitrogen in the perhydro series (Fig. 2). These effects are also apparent to a lesser extent in the chloro derivatives of pyridine.
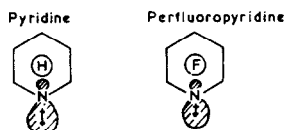

Fig. 2. Representation of sp² orbital (exaggerated) occupied by the "lone pair" in pyridine and perfluoropyridine.

The total dipole, μ_{total}, is the vector sum of μ_Q and $\mu_{hyb.}$ and it is clear from Table 1 that these two components are not necessarily in the same direction. In the case of the chloro derivatives, the agreement between the calculated and experimental dipole moments is less good and this almost certainly arises from the less satisfactory approximations and parametrisations for second-row atoms within the CNDO formalism.

Basicities

Protonation of the heterocyclic bases may be written as

$$B + H_3O^+ \rightleftharpoons BH^+ + H_2O \tag{2}$$
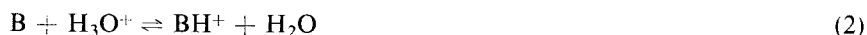
and the acidity constant, K_a, for the base is given by

$$K_a = \frac{a_B \, a_{H_3O^+}}{a_{BH^+}} \tag{3}$$

where a_B, $a_{H_3O}^+$ and a_{BH}^+ are the activities of the respective molecules and ions and the activity of water is taken as unity.

The equilibrium constant, K_{eq}, may be expressed as

$$K_{eq} = f \times e^{-\Delta E_0^\circ/RT} \qquad (4)$$

where f is the ratio of the partition functions of BH^+, B and H_3O^+, and ΔE_0^0 is the difference in internal energy of 1 mol of the products and 1 mol of the reactants in their standard states at 0 K. Now ΔE_0^0 represents the difference in energy calculated from the zero-point energies of the products and the reactants. Since the zero-point energies for the reactants and the products will be similar in magnitude and also small compared to ΔE_0^0, then to a good degree of approximation ΔE, the energy difference corresponding to energy minima on the relevant potential-energy surface, may be used instead of ΔE_0^0.

The equilibrium constant, K_{eq}, may therefore be written as

$$K_{eq} = f \times e^{-\Delta E/RT} \qquad (5)$$

It will also be seen that

$$K_a = 1/K_{eq} \qquad (6)$$

and that

$$pK_a = -pK_{eq} \qquad (7)$$

The term ΔE in the equilibrium constant may be split into two terms ΔE_g and $\Delta E_{solv.(T)}$, where the latter term is temperature-dependent[10]. The equilibrium constant may then be expressed as

$$K_{eq} = f \times \exp{-(\Delta E_g + \Delta E_{solv.(T)})/RT} \qquad (8)$$

The term $\Delta E_{solv.(T)}$ may be expressed as

$$\Delta E_{solv.(T)} = \Delta E_{cav.} + \Delta E_{orient.} + \Delta E_{disp.} + \Delta E_{iso.} + \Delta E_{aniso.} \qquad (9)$$

For molecules or ions of similar shape and size, it may be shown that all these terms are essentially constant, and therefore since for similar molecules f will also essentially be constant[11]

$$\ln K_{eq} \propto -\Delta E_g \qquad (10)$$

and

$$pK_a \propto -\Delta E_g \qquad (11)$$

ΔE_g represents the energy difference between the isolated base and conjugate acid, and values computed within the CNDO/2 formalism are given in Table 4. It may be noted that the value of ΔE_g calculated here in the case of pyridine is in good agreement with the value of the proton affinity (-941 ± 9 kJ mol^{-1}) obtained by ion-cyclotron resonance studies[12].

In Figure 3 the pK_a values, for monoprotonation, given in Table 4 have been plotted against the corresponding ΔE_g values obtained from the calculations. It is apparent that although there is no exact correlation, there is a general "trend"

observable indicated by the broken line. The lower end of this trend line was decided to accord with the observation that perfluoropyridazine ($\Delta E_g = -1200$ kJ mol^{-1}) is more basic than perfluoropyridine ($\Delta E_g = -1214$ kJ mol^{-1}).
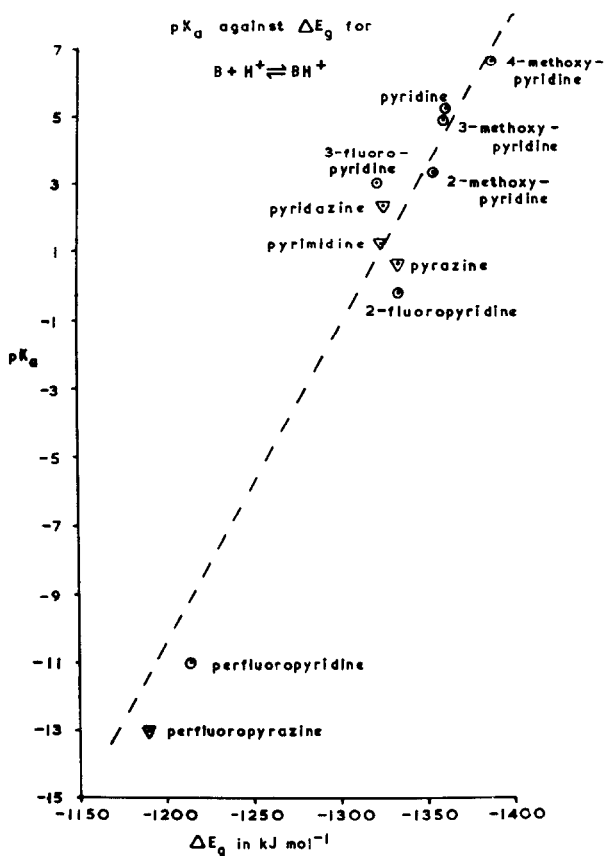

Fig. 3. Plot of pK_a and energy release on protonation in the gaseous phase (ΔE_g).

The slope of the "trend" line in Figure 3 may be compared with the value expected from a consideration of equations (5) and (7).

The value obtained from Figure 3 is ΔpK_a of 1 for $\Delta\Delta E_g$ of 10 kJ mol^{-1} whilst equations (5) and (7) give a ΔpK_a value of 1 for a $\Delta\Delta E$ value of ca. 6 kJ mol^{-1} at 300 K. In view of the approximations that have been made in obtaining the values of ΔE_g and ΔE, the agreement is quite reasonable. Furthermore, it suggests that though the absolute values of ΔE_g may not correspond to the absolute values of ΔE, the differences in energy for the different compounds considered are of the correct magnitude. In order to obtain a better correlation there is a need to consider

$\Delta E_{\mathrm{solv.}(T)}$, since for small differences in ΔE_g differences in $\Delta E_{\mathrm{solv.}(T)}$ may be of the same order of magnitude and are not necessarily of the same sign. This is probably more important when considering different series of compounds.

When diprotonation of the three diazines is considered, reference to Table 4 shows that the values of ΔE_g are, in general, approximately half the values for monoprotonation. Using then the trend shown in Figure 3, it would appear that diprotonation would be extremely difficult and that the pK_a values would be large and negative $(<< -20)$. This does not agree with data in the literature which suggest a pK_{a_2} value for pyrazine and pyrimidine of -5.8 and -6.3 respectively[14, 15].

TABLE 4

ENERGY DIFFERENCES AND pK_a VALUES FOR SOME OF THE FLUORO, CHLORO AND METHOXY DERIVATIVES OF PYRIDINE, PYRIDAZINE, PYRIMIDINE AND PYRAZINE ON PROTONATION
(i) $H^+ + B \rightleftharpoons HB^+$

Base		$pK_a{}^a$	ΔE_g/kJ mol^{-1}
Pyridine		5.22	—1361
2-Fluoropyridine		—0.22	—1334
3-Fluoropyridine		2.97	—1322
4-Fluoropyridine		—	—1345
2K-methoxypyridine		3.28	—1354
3K-methoxypyridine		4.88	—1360
4K-methoxypyridine		6.62	—1388
Perfluoropyridine		(—11)^b	—1214
Perchloropyridine		—	—1254
Pyridazine		2.3	—1325
Perfluoropyridazine		—	—1200
Pyrimidine		1.3	—1324
Perfluoropyrimidine		—	—1198
Pyrazine		0.6	—1333
2-Fluoropyrazine	(4)	—	—1290
	(1)	—	—1305
Perfluoropyrazine		(—13)^b	—1189

(ii) $HB^+ + H^+ \rightleftharpoons H_2B^{2+}$

Base	pK_{a_2}	ΔE_g/kJ mol^{-1}
1-H-Pyridazine	—	—609.5
1-H-Perfluoropyridazine	—	—527.3
1-H-Pyrimidine	(—6.3)^c	—689.0
1-H-Perfluoropyrimidine	—	—592.4
1-H-Pyrazine	(—5.78)^c	—696.0
4-H-2-Fluoropyrazine	—	—679.7
1-H-2-Fluoropyrazine	—	—664.8
1-H-Perfluoropyrazine	—	—589.4

^{a} pK_a values for $HB^+ + H_2O \rightleftharpoons B + H_3O^+$, taken from ref. 13.
^{b} Taken from ref. 16.
^{c} Taken from refs. 14, 15.

However, since solvation energy terms for singly- and doubly-charged ions would be expected to be somewhat different, the same correlation would not necessarily apply for both mono- and di-protonation. It is not entirely clear, though, that the results reported for pyrazine and pyrimidine refer to the protonation of the mono-protonated species, since for perfluoropyrazine it has been suggested that the addition of further acid to the monoprotonated species may lead to the formation of a radical dication rather than to diprotonation[16].

Electronic charge distribution and basicities

There is no apparent correlation between the basicity of the compounds considered and the calculated electronic charge on the nitrogen before protonation, as is clearly evident from Figures 4–6. A correlation would imply an "early" transition state, that is a transition state that "looked like" a proton approaching the base. Since however the bases considered are all known to be weak, it is more likely that the transition state "looks" more like the protonated species. A correlation between the basicity and the electronic charge on the nitrogen would therefore not be expected.

On protonation the positive charge is considerably delocalised. The calculations suggest that for the ring atoms the charge is mainly distributed as positive π charge on the atoms *ortho* and *para* to the protonated nitrogen. Diprotonation results in differences between the three diazines in terms of charge distribution becoming more marked. Thus the σ and π charges on the nitrogens are increased in magnitude, compared to monoprotonation, in the case of pyridazine. In the case of pyrimidine, there is very little change when comparing the charges of the protonated nitrogens, and for pyrazine the charges are less on the nitrogens in the diprotonated species. Also in pyrimidine the carbon atom in the *meta* position shows little effect on the σ and π charges either on mono- or di-protonation.

Nucleophilic substitution by methoxide ion

The reaction considered here, the substitution of fluoride (and in some cases chloride ion) by methoxide ion is known, in general, to be irreversible under the experimental conditions employed. The products of the reaction are therefore kinetically-controlled. The rate constant for the reaction is given by

$$k_r = (kT/h)f \times e^{-\Delta E_0^*/RT} \tag{12}$$

where k_r is the rate constant, k is Boltzmann's constant, h is Planck's constant, ΔE_0^* is the energy of activation and f is the ratio of the partition functions of the transition state and the reactants. ΔE_0^* differs from the potential energy of activation, ΔE^*, in the zero-point energy difference between the reactants and the transition-state complex. Writing ΔE_z^* for this zero-point energy difference, equation (12) may be written

$$k_r = (kT/h)f \times e^{-(\Delta E^* + \Delta E_z^*)/RT} \tag{13}$$

where ΔE^* is the potential energy of activation.
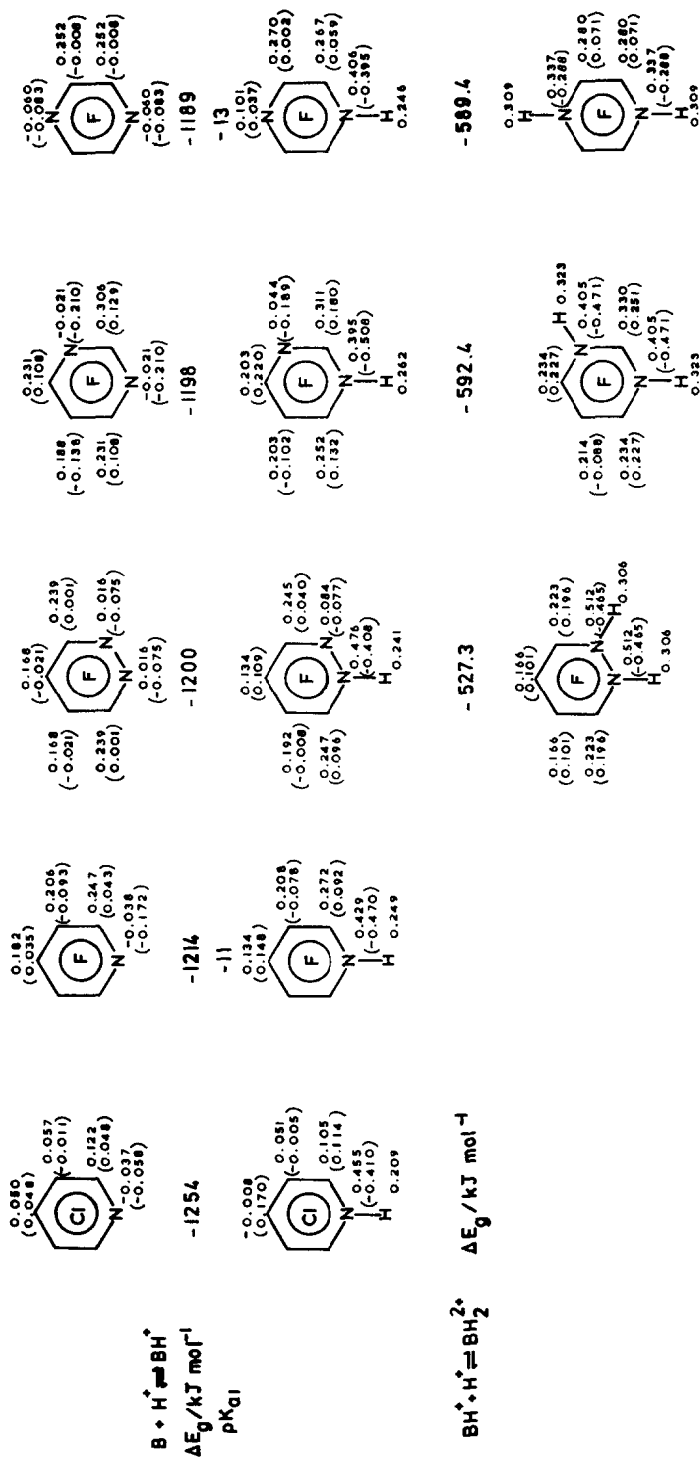
Fig. 4. σ and π Charges for the ring atoms and σ charges for the hydrogen attached to nitrogen, π charges being the values in brackets.

Fig. 5. σ and π Charges for the ring atoms and σ charges for the hydrogen attached to nitrogen, π charges being the values in brackets.
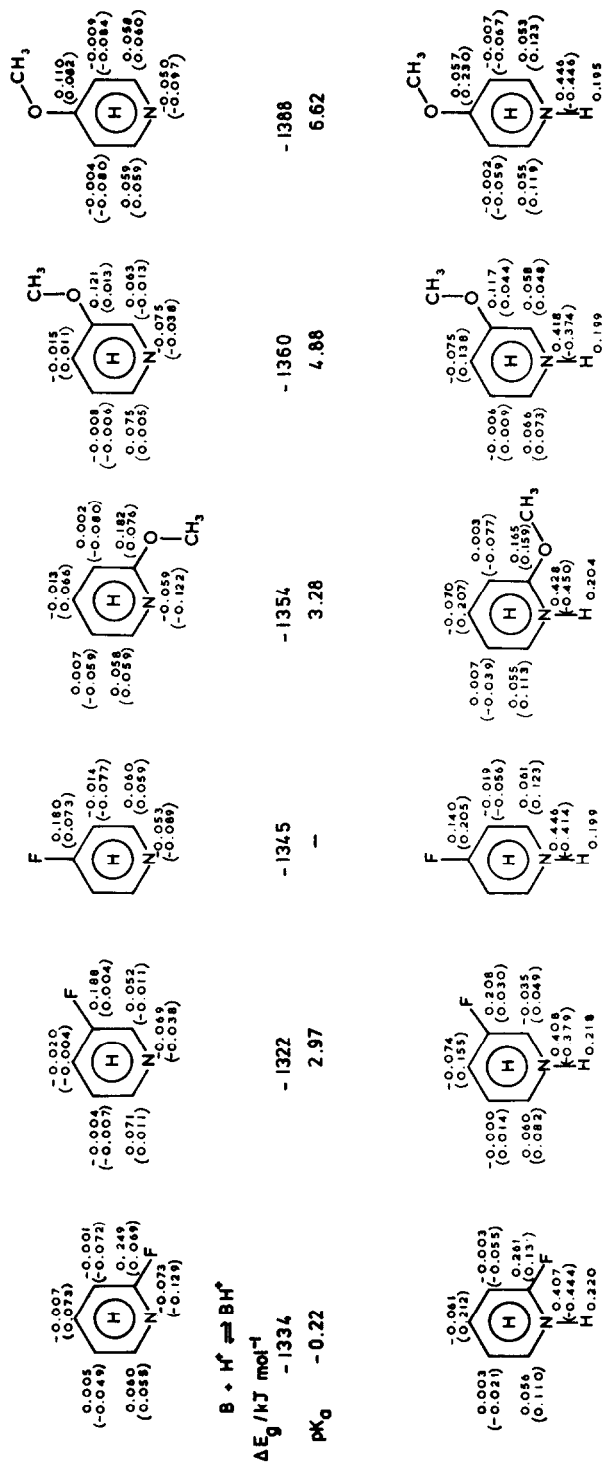
Fig. 6. σ and π Charges for the ring atoms and σ charges for the hydrogen attached to nitrogen, π charges being the values in brackets.

For the reaction of two molecules, or of two sites within the same molecule, relative rates for the reactions may be written

$$k_{r_1}/k_{r_2} = f_1/f_2 \times e^{-\Delta(\Delta E^* \div \Delta E_z^*)/RT} \tag{14}$$

Now for two similar reacting molecules ΔE_z^* may be presumed to be very similar for both and $\Delta\Delta E_z^*$ may therefore be taken as being very small. Therefore equation (14) may be written as

$$k_{r_1}/k_{r_2} = f_1/f_2 \times e^{-\Delta\Delta E^*/RT} \tag{15}$$

Since for a reaction in solution

$$\Delta H_0^* = \Delta E_0^* + nRT \tag{16}$$

and

$$\Delta H_0^* = E_a - RT \tag{17}$$

where E_a is the Arrenhius activation energy in

$$k_r = Ae^{-E_a/RT} \tag{18}$$

it follows that at the same temperature

$$\Delta E_a \approx \Delta\Delta E_0^* \approx \Delta\Delta E^* \tag{19}$$

Therefore differences in the potential energy of activation may be equated with differences in the Arrenhius energy of activation (see below).

$\Delta\Delta E^*$ may be expressed as

$$\Delta\Delta E^* = \Delta\Delta E_g + \Delta\Delta E_{solv.} \tag{20}$$

and $\Delta\Delta E_{solv.}$ written as

$$\Delta\Delta E_{solv.} = \Delta\Delta E_{cav.} + \Delta\Delta E_{orient.} + \Delta\Delta E_{disp.} + \Delta\Delta E_{iso.} + \Delta\Delta E_{aniso.} \tag{21}$$

As before, the various terms making up $\Delta\Delta E_{solv.}$ may be shown to be essentially constant within a similar series, and therefore $\Delta\Delta E_{solv.}$ may be taken as approximately zero. Equation (15) may then be put as

$$k_{r_1}/k_{r_2} = f_1/f_2 \times e^{-\Delta\Delta E_g/RT} \tag{22}$$

It is clear from the kinetic studies of Burdon and co-workers[17] and of Liveris and Miller[18] that relative rate constants for nucleophilic displacements of fluorine and chlorine in molecules of similar electronic structure is determined predominantly by the exponential term, the ratio of partition functions varying to only a relatively small extent. It should therefore be possible to use $\Delta\Delta E_g$ as a means of comparing the reactivities of similar series, or of different sites within the same molecule.

The calculation of ΔE_g for the isolated species requires a knowledge of the geometries of the reactants and an appropriate model for the transition state. In this work we have considered a dynamic model in discussing reactivities and the transition states have therefore been approximated as the relevant Wheland (σ complex) intermediates.

The results of these calculations expressed as energy differences are shown in Figure 7. Where appropriate, Arrhenius activation-energy differences have also been included (values in brackets)[17-19]. In general, considering the approximations involved, the agreement between theory and experiment is quite satisfactory. Also shown in Figure 7 are calculated charge distributions for the ring atoms in the Wheland intermediates. Calculations referring to the methoxy-substituted compounds are given in Table 5.

TABLE 5

ENERGY DIFFERENCES BETWEEN REACTANTS AND WHELAND INTERMEDIATES FOR REACTION WITH METHOXIDE ION

Reactant	P[a]	ΔE_g/kJ mol^{-1}
4K-methoxyperfluoropyridine	2	—753.7
	3	—673.7
3K-methoxyperfluoropyridazine	4	—723.3
	5	—723.5
	6	—704.8
4A-methoxyperfluoropyridazine	3[b]	—735.2
	5	—754.0
	6	—545.6
2K-methoxyperfluoropyrimidine	4	—779.6
	5	—554.8
4K-methoxyperfluoropyrimidine	2	—765.2
	5	—554.2
	6	—778.2
5K-methoxyperfluoropyrimidine	2	—768.4
	4	—835.1
2K-methoxyperfluoropyrazine	3	—739.3
	5	—738.0
	6	—737.7

[a] P = Position of substitution.
[b] Orientation of methoxy group is 4K in intermediate as this is the position of lowest energy.

One effect of ignoring solvation energies (see above) is that the energy of the reactants is calculated to be higher than that of the intermediate. Therefore when comparing reactivities the intermediate with the largest negative value of ΔE_g will correspond to the greatest reactivity.

The results of some of these calculations are shown in Figure 7, together with the charges calculated for the ring atoms. The calculations of ΔE_g for methoxy-substituted compounds are given in Table 5.

The results show that for benzene and monochloropyridine the calculated results agree reasonably well with the known differences in the activation ener-

ΔE_g   ΔΔE_g   ΔΔE_g

- 714.3   45.7   135.3
                                          (63.5)

-650.9   6.3   96.3

-737.1   7.3   85.7
                   (16)   (32)

-784.5   9   128.2

-921.4   15.8   66.7

-743.1   17.1

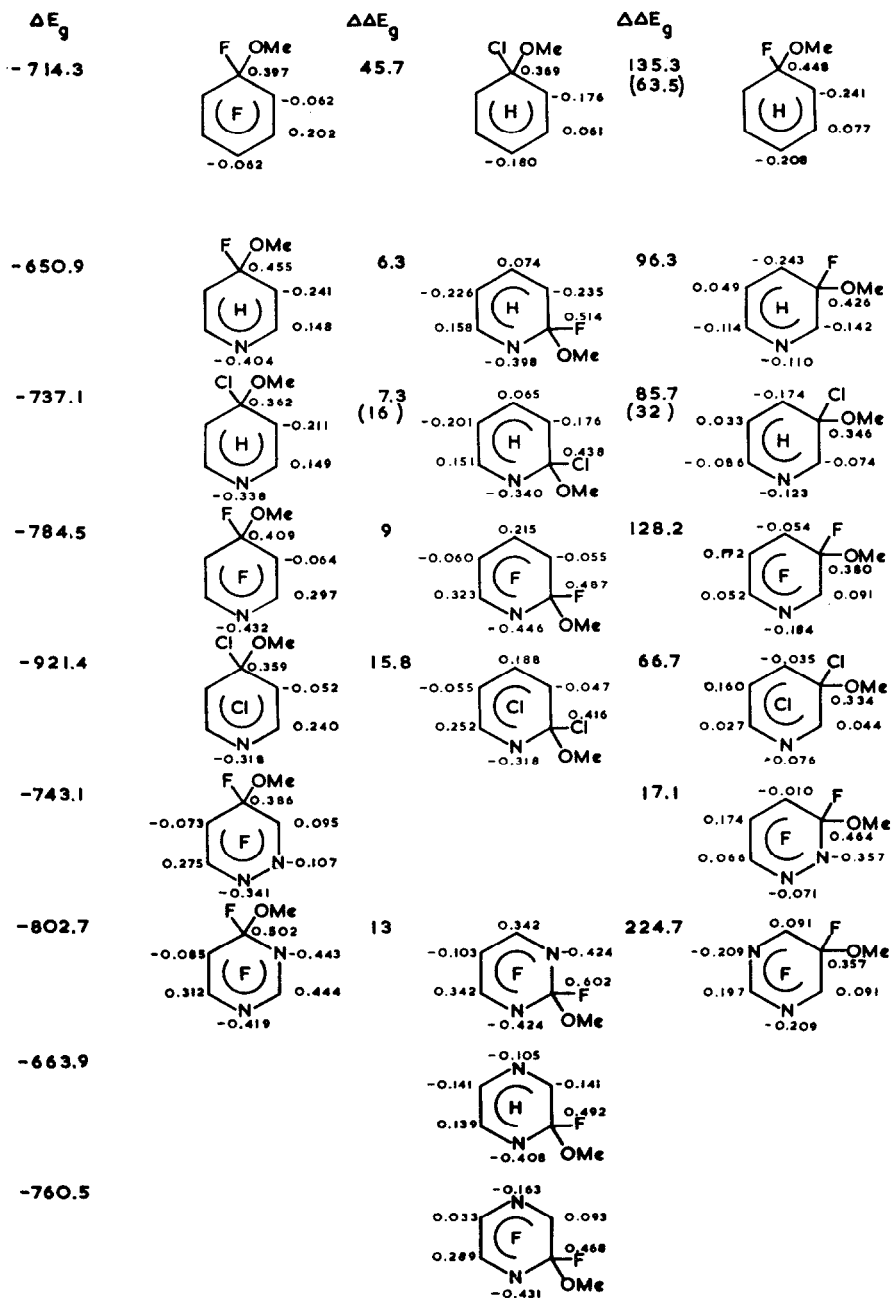-802.7   13   224.7

-663.9

-760.5

Fig. 7. Charges on ring atoms in the Wheland intermediates and energy differences between reactants and intermediate. Values in brackets refer to experimentally-determined differences in Arrhenius activation energies. $\Delta\Delta E_g$ values refer to energy differences between the intermediate to the right and the one on the extreme left (ΔE_g). ΔE_g and $\Delta\Delta E_g$ are both in kJ mol^{-1}.

gies [17-19]. That the agreement is not better is due partly to the approximations made in the calculations and to the fact that the calculations are for the Wheland intermediate while the activation energies are for the transition state. Considering all the results in Figure 7, it is seen that a fluorine (or chlorine) that is attached to a carbon that is *para* to a nitrogen is more readily replaced than an *ortho* fluorine (or chlorine) with $\Delta\Delta E_g \approx 10$ kJ mol^{-1}. A *meta* fluorine is seen to be very difficult to replace by methoxide ion compared to a *para* fluorine with $\Delta\Delta E_g \approx 100$ kJ mol^{-1}. In the case of pyrimidine, a fluorine atom at position 5 is in a position *meta* to two nitrogen atoms and not surprisingly $\Delta\Delta E_g \approx 200$ kJ mol^{-1}. This order of reactivity is in full agreement with experimental observations [1, 20, 21]. The calculations are not, however, capable of predicting the proportions of *ortho* and *para* products formed during monosubstitution (virtually no *meta* product is formed). Thus from the calculated energy differences it would be expected that the *ortho/para* ratio would be greater for perfluoropyridine ($\Delta\Delta E_g = 9$ kJ mol^{-1}) than for perchloropyridine ($\Delta\Delta E_g = 15.8$ kJ mol^{-1}). The experimental data, however, show that perfluoropyridine gives exclusively the *para* product [22] while perchloropyridine gives 2-methoxy- as well as 4-methoxy-perchloropyridine [23].

It is possible to make predictions concerning the relative reactivities between benzene, pyridine and the diazines. However when this is done inconsistencies arise when the predictions are compared to the known order of reactivities. These inconsistencies are probably due to the neglect of the solvation-energy terms since for different series it cannot be assumed that the various terms involved in the solvation-energy expression [equation (21)] are the same for the different series. Thus calculations give the ordering of energy differences in Figure 8, but experimental observation [24] shows that perfluoropyridazine is more reactive than perfluoropyridine. A similar result is found for the chloro- and fluoro-pyridines. The calculations suggest that a chloropyridine should be more reactive than the corresponding fluoropyridine but experimental observations indicate the converse to be true.

$\Delta\Delta E_g$ -88   -70   -46   -29   (0)   kJ mol^{-1}
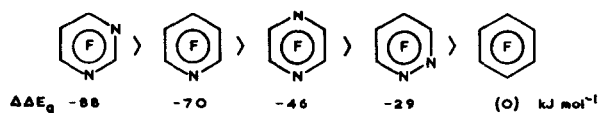
Fig. 8. Relative reactivities as suggested by $\Delta\Delta E_g$ values.

When the results in Table 5 are considered together with the energies in Figure 7, the effect of introducing a methoxy group on the further reactivity of the compounds considered can then be seen. If the methoxy group is in an *ortho* position with respect to any nitrogen, then the value of ΔE_g is approximately 20 kJ mol^{-1} more positive for substitution at any site compared to the same site in the parent compound. Thus the effect is to make the compound less reactive towards nucleophilic substitution of fluorine by methoxide ion. When the methoxy

group is situated *meta* to a nitrogen, then the positions *ortho* to the methoxy are more reactive, with ΔE_g values 10 and 30 kJ mol^{-1} respectively more negative than the corresponding positions in the parent compounds. A position *para* to the methoxy will however be less reactive, with ΔE_g approximately 20 kJ mol^{-1} more positive than in the parent compound. Position 6 in 4-methoxyperfluoropyridazine is interesting since ΔE_g is 180 kJ mol^{-1} more positive than position 6 in perfluoropyridazine. This position is *meta* with respect to the methoxy and *meta* and *para* with respect to the nitrogens, and the value of ΔE_g suggests that substitution at position 6 will be extremely unlikely to occur. The value of ΔE_g is in fact very similar to that for position 5 in the perfluoropyrimidines which is known to be very difficult to replace. When the results for 4-methoxyperfluoropyridine are considered, it is seen that a position that is *ortho* with respect to the methoxy and *meta* to the nitrogen is more reactive than the same position in the parent compound, while a position *ortho* to the nitrogen is less reactive.

The above may be summarised briefly as follows:

The introduction of a methoxy group into perfluoropyridine or into a perfluorodiazine makes a position *ortho* to the methoxy group more reactive ($\Delta\Delta E_g \approx$ 10–30 kJ mol^{-1}) with respect to nucleophilic substitution of fluorine by methoxide ion than the same position in the parent molecule provided that the position is not also *ortho* to a nitrogen atom. In all other cases the position will be less active than in the parent compound, usually with $\Delta\Delta E_g$ approximately 20 kJ mol^{-1}.

Charge distribution in Wheland intermediates

In Figure 7 it is seen that when a nitrogen atom lies *ortho* or *para* to the position at which substitution is taking place it bears a larger negative charge than a *meta* nitrogen. This suggests that the charge on the nitrogen is connected with the energy difference since *ortho*- and *para*-fluorine atoms are more readily replaced than *meta*-fluorine atoms. The connection is not, however, simple since an *ortho* nitrogen generally bears a larger negative charge than a *para* nitrogen yet the relative ease of replacement of the fluorines is the converse. The charge distributions do not agree therefore with the suggestion that the *para*-"quinoid" structure for the Wheland intermediate is of lower energy than the *ortho* structure because the *para* nitrogen bears a larger portion of the negative charge introduced.

CONCLUSIONS

All-valence-electron SCF–MO CNDO/2 calculations give energies for molecules and intermediates formed from them that enable relative reactivities of a series of compounds or of sites within a molecule to be calculated that are in reasonable agreement with experimental data. Furthermore, the energy differences calculated correspond reasonably closely to the known energy differences (see the

sections on basicities and nucleophilic substitution) for the reactions. When the compounds are not from the same series, for example perfluoro- and perchloro-pyridine, then solvation energies must also be considered since the calculated reactivities are not entirely consistent with the experimental observations. The electronic-charge distributions agree in general with what might be expected from the electronegativities of the atoms. The computed dipole moments in the case of the perhydro and perfluoro derivatives are in good agreement with the experimental results.

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