# 654. The $S_N$ Mechanism in Aromatic Compounds. Part XXVIII.[1] Reactivity in the Pyridine Ring System.

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Rates of reaction of the chloropyridines and their *N*-oxides with sodium methoxide in absolute methanol have been measured, and the rates of reaction of the chloro-1-methylpyridinium compounds with this reagent estimated from the measurements with sodium *p*-nitrophenoxide.

The rate or free-energy order of position reactivity is $4 > 2 > 3$ for the pyridines and their *N*-oxides, and $2 > 4 > 3$ for the pyridinium compounds. The order of $E_{act}$ is $4 < 2 < 3$ in all cases.

The order of ring substituent (=$X^-$) reactivity is $N^+$–Me > $N^+$–$O^+$ > N > C–H in all positions. The order of $E_{act}$ is correspondingly in the reverse order except for the approximate equality for $N^+$–Me and $N^+$–$O^-$ in the 3-position.

Reactivities are given in terms of substituent rate factors and Hammett substituent constants and discussed in detail. The values of the latter are up to 2·492, believed to be the highest value ever recorded.

Reactivity in pyridine and pyridinium compounds has been referred to briefly by one of us,[2] and we have since published results for pyridinium compounds [3] with special reference to the light these throw on the positional order of the inductive effect. There has been special interest in recent years in N-oxides (see, *e.g.*, refs. 4—6).

We now present kinetic results for methanolysis of a complete series of monochloropyridines, pyridine *N*-oxides, and 1-methylpyridinium compounds. These are compared with each other and with results for chlorobenzene.[7] The latter comparison thus shows also the effect of substituting nitrogen in various forms into the benzene ring.

Rates of reaction, and derived quantities, for the reaction of sodium methoxide in absolute methanol with 2-, 3-, and 4-chloropyridine and their *N*-oxides have been measured, and have been computed for the 2-, 3-, and 4-chloropyridinium compounds from the corresponding measurements with sodium *p*-nitrophenoxide in methanol by using the relationship obtained with 1-chloro-2,4-dinitrobenzene;[8] differences there are: $E_{act}$ —4·6 kcal. mole$^{-1}$; $\log_{10} B$ +0·9; $S_{act}$ +4·1 e.u.; $k_2$ at 50°, $1{\cdot}104 \times 10^4$.

The positional order of reactivity is $4 > 2 > 3$ for the pyridines and their *N*-oxides and $2 > 4 > 3$ for the 1-methylpyridinium compounds, but the change over of relative reactivity at the 2 and 4 positions is consequent on a high entropy of activation for the 2-chloropyridinium compound. The $E_{act}$ order in all cases is $4 < 2 < 3$.

The ring substituent (=X–) order of reactivity is $N^+$–Me > $N^+$–$O^+$ > N > C–H. The $E_{act}$ values are correspondingly in reverse, except for $N^+$–Me and $N^+$–$O^-$ in the 3-position which are approximately equal.

Experimental and derived data are given in Tables 1—4. Reactivities are compared in the form of substituent rate factors (S.R.F) [9] and Hammett substituent constants ($\sigma^*$),[10] the reaction constant ($\rho$) [10] being taken from the work of Miller and Wan.[7]

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[1] Part XXVII, Miller, *J. Amer. Chem. Soc.*, 1963, **85**, in the press.

[2] Miller, *Rev. Pure Appl. Chem.* (*Australia*), 1951, **1**, 171.

[3] Liveris and Miller, *Austral. J. Chem.*, 1958, **11**, 297.

[4] Katritzky, *J.*, 1956, 2404 and subsequent papers.

[5] (*a*) den Hertog and Overhoff, *Rec. Trav. chim.*, 1950, **69**, 468; (*b*) den Hertog and Combe, *ibid.*, 1951, **70**, 581; (*c*) 1952, **71**, 745.

[6] (*a*) Ochiai, Teshigawara, Oda, and Naito, *J. Pharm. Soc. Japan*, 1944, **64**, 5/6*A*, 1; (*b*) Ochiai, *J. Org. Chem.*, 1953, **18**, 534.

[7] Miller and Wan, following paper.

[8] Leahy, Liveris, Miller, and Parker, *Austral. J. Chem.*, 1956, **9**, 382.

[9] Miller, *J.*, 1952, 3550.

[10] Hammett, (*a*) *J. Amer. Chem. Soc.*, 1937, **59**, 96; (*b*) *Trans. Faraday Soc.*, 1938, **34**, 156; (*c*) Jaffé. *Chem. Rev.*, 1953, **53**, 191; (*d*) Miller, *Austral. J. Chem.*, 1956, **9**, 61.

## EXPERIMENTAL

*Materials.*—2-*Chloropyridine.* The commercial product was purified by distillation.

3-*Chloropyridine.* 3-Aminopyridine was prepared from nicotinamide by the Hoffman reaction [11] and converted into the chloro-compound by the Gattermann reaction.[12]

4-*Chloropyridine.* This was obtained by reduction of the *N*-oxide with iron powder and acetic acid.[5b]

2-*Chloropyridine* N-*oxide.* At the time of preparation this substance had not been described. We used a slight modification of the procedures described by den Hertog and Combe [5b] and Ochiai [6b] which is almost identical with that of Katritzky.[13] Our product (15 g., 66%) was a white, extremely hygroscopic solid. It was purified by distillation (b. p. 110°/2 mm.). The analyst reported it as too hygroscopic for accurate analysis (Found: C, 44·8; H, 3·7; O, 14·4. Calc. for $C_5H_4ClNO$: C, 46·5; H, 3·1; O, 12·35%).

3-*Chloropyridine* N-*oxide.* This was unknown at the time of preparation but has since been reported by Shindo.[14] Our product (7 g., 60%) obtained similarly to the 2-chloro-compound was extremely hygroscopic and was purified by distillation (b. p. 92°/1·5 mm.).

TABLE 1.

Experimental rate constants, and some derived parameters, for reaction of sodium methoxide in methanol with (*a*) monochloropyridines and (*b*) their *N*-oxides; and of sodium *p*-nitrophenoxide in methanol with (*c*) monochloropyridinium compounds. Estimated values for methanolysis of (*c*) are given in square brackets.

| | $k_2$ (l. mole$^{-1}$ sec.$^{-1}$) at temperature shown in parenthesis and at ionic strength ($\mu$) = 0. | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Position Cl | (*a*) Experimental | | | (*b*) Calculated at 0° | 50° | 100° | $E_{act}$ kcal. mole$^{-1}$ | $\log_{10} B$ | $S_{act}$ (e.u.) |
| (*a*) Pyridines 2 | 1·12; 1·13 $\times 10^{-4}$ (121·2°) | 2·72; 2·74 $\times 10^{-4}$ (130·9°) | 5·42; 5·52 $\times 10^{-4}$ (138·8°) | 8·71 $\times 10^{-12}$ | 3·31 $\times 10^{-8}$ | 1·38$_5$ $\times 10^{-5}$ | 28·9 | 12·1 | −5·33 |
| 3 | 2·82; 2·85 $\times 10^{-4}$ (211·5°) | 5·08; 5·11 $\times 10^{-4}$ (220·0°) | 7·66; 7·71 $\times 10^{-4}$ (226·0°) | 9·33 $\times 10^{-16}$ | 1·09 $\times 10^{-11}$ | 1·05 $\times 10^{-8}$ | 32·8$_5$ | 11·2$_5$ | − 9·21 |
| 4 | 1·78; 1·82 $\times 10^{-4}$ (100·8°) | 4·48; 4·48; 4·45 $\times 10^{-4}$ (111·2°) | 9·30; 9·58 $\times 10^{-4}$ (120·0°) | 6·59 $\times 10^{-10}$ | 8·91 $\times 10^{-7}$ | 1·67$_5$ $\times 10^{-4}$ | 25·2 | 11·0 | −10·4 |
| (*b*) Pyridine *N*-oxides 2 | 3·88; 3·95 $\times 10^{-4}$ (45·25°) | 1·69$_5$; 1·73 $\times 10^{-3}$ (60·4°) | 9·67; 9·88 $\times 10^{-3}$ (80·7°) | 1·95 $\times 10^{-6}$ | 6·40 $\times 10^{-4}$ | 4·43 $\times 10^{-2}$ | 20·3 | 10·55 | −12·4 |
| 3 | 2·06; 2·14 $\times 10^{-4}$ (100·8°) | 1·04$_5$; 1·06 $\times 10^{-3}$ (120·0°) | 4·30; 4·45 $\times 10^{-3}$ (138·4°) | 1·04 $\times 10^{-9}$ | 1·16 $\times 10^{-6}$ | 1·97 $\times 10^{-4}$ | 24·6 | 10·7 | −11·7 |
| 4 | 2·33; 2·40 $\times 10^{-4}$ (35·0°) | 9·37; 9·53 $\times 10^{-4}$ (48·9°) | 4·00; 4·08 $\times 10^{-3}$ (66·0°) | 4·44 $\times 10^{-6}$ | 1·00 $\times 10^{-3}$ | 5·27 $\times 10^{-2}$ | 19·0 | 9·8$_5$ | −15·6 |
| (*c*) Pyridinium compounds 2 | 6·91; 6·99 $\times 10^{-2}$ (0·0°) | 2·32; 2·35 $\times 10^{-1}$ (10·1°) | 5·63; 5·76 $\times 10^{-1}$ (17·9°) | — | 1·39 $\times 10^{1}$<br>[1·53$_5$ $\times 10^{5}$] | — | 18·5$_5$<br>[13·9$_5$] | 13·7<br>[14·6] | +2·00<br>[+6·11] |
| 3 | 1·22; 1·24 $\times 10^{-3}$ (120·0°) | 3·50; 3·56 $\times 10^{-3}$ (131·0°) | 7·11; 7·21 $\times 10^{-3}$ (138·8°) | — | 2·84 $\times 10^{-7}$<br>[3·14 $\times 10^{-3}$] | — | 30·2<br>[25·6] | 13·9<br>[14·8] | +2·91<br>[+7·03] |
| 4 | 9·58; 9·78 $\times 10^{-3}$ (10·1°) | 4·53; 4·57 $\times 10^{-2}$ (25·0°) | 1·23; 1·26 $\times 10^{-1}$ (35·3°) | — | 4·60 $\times 10^{-1}$<br>[5·08 $\times 10^{-3}$] | — | 17·6<br>[13·0] | 11·5$_5$<br>[12·4$_5$] | −7·84<br>[−3·73] |
| (*d*) 2-, 3-, and 4- −CH= (Chlorobenzene) | — | — | — | — | 1·20 $\times 10^{-16}$ | | 39·9$_5$ | 11·1 | −9·90 |

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[11] Allen and Wolf, *Org. Synth.*, 1950, **30**, 3.

[12] Rath, *Annalen*, 1931, **486**, 100.

[13] Katritzky, *J.*, 1957, 191.

[14] Shindo, *Chem. Pharm. Bull.* (*Japan*), 1958, **6**, 117.

4-*Chloropyridine* N-*oxide*. By the methods of den Hertog and Combe [5b] and of Ochiai,[6b] the 4-nitro-compound gave a product, m. p. 152—153°, that after distillation had m. p. 188—189° (lit., 152—153°,[11] 169·5°,[5b] 187—189° [6b]) [Found: (*a*) m. p. 152—153°: C, 46·55; H, 3·0; Cl, 26·4. (*b*) m. p. 188—189°: C, 46·4; H, 3·3; Cl, 27·6%].

2-, 3-, and 4-*Chloro*-1-*methylpyridinium compounds*. The preparation of these compounds has been described by Liveris and Miller.[3]

*Kinetic Procedure*.—Runs were carried out with equimolar concentrations of the heterocyclic compound and sodium methoxide in absolute methanol. Rate constants ($k_2$) were obtained by graphical plots after potentiometric estimation of chloride in aliquot parts quenched in dilute chloride-free nitric acid. Checks of methoxide consumption were made potentiometrically. The values of activation energy ($E_{act}$) were determined by least-squares analysis of all determined values of $\log_{10} k_2$ ($\nless 6$) and reciprocal temperature. The values of the frequency factor ($\log_{10} B$) and entropy of activation ($S_{act}$) were then computed. Estimated errors based on reproducibility of rates to $\pm 1\frac{1}{2}\%$ and $E_{act} = \pm 0{\cdot}4$ kcal. mole$^{-1}$; $\log_{10} B = \pm 0{\cdot}3$; $S_{act} = \pm 1$ e.u.

Special precautions were taken with the very hygroscopic 2- and 3-chloropyridine *N*-oxide. They were distilled at reduced pressure directly into dried weighed flasks, which were then sealed and reweighed. The methanol was then added for kinetic runs. As a check, amounts of chloride ion at 100% reaction were estimated.

Reactions of the 2-, 3-, and 4-chloro-2-methylpyridinium compounds with sodium *p*-nitrophenoxide have been described; [3] the corresponding rates and derived data for methanolysis were estimated as explained above.

Kinetic data are given in Table 1.

## DISCUSSION

Heterocyclic systems such as pyridine and its derivatives are fully aromatic. In comparison with benzene, the substitution of the more electronegative nitrogen for =CH– results in a greater than average (for the ring) electron density on nitrogen and a corresponding reduction on the ring-carbon atoms (pyridine has a dipole moment =2·23 D [15]). More particularly, since $\pi$ as well as $\sigma$ electron systems are involved, electron density is least on 2- and 4-positions.

As a consequence, the energy of formation of $S_E$ transition states is raised and of $S_N$ transition states [1,2,16,17] lowered relative to benzene. The deactivation for $S_E$ reactions is well known, though at first it was not well recognised that part of this was due to reaction of the pyridines as the conjugate acids in highly acidic media.

The corresponding activation for $S_N$ reactions [2] has been less investigated, although Chichibabin [18] recorded the formation of 2-aminopyridine by amidation in 1914. More recently Chapman and his co-workers have carried out extensive kinetic investigations, mainly with electrically neutral nucleophiles,[19] but also have made some measurements with ethoxide on 2- and 4-chloropyridines.[20] The results of the latter are similar to, but do not exactly parallel, ours with methoxide.

The significance of the *N*-oxide group as one which facilitates both $S_E$ and $S_N$ reactions is now well realised; [4-6] Miller and Parker [21] have included it in commenting on a number of such dual activating groups and some further work has been carried out.[22]

Brown and Heffernan [23] have made quantum-mechanical calculations of pyridine reactivity by the molecular-orbital method and from $\pi$-electron densities and localisation energies predicted the position order $2 > 4 > 3$, with 2 and 4 relatively close. Jaffé,[24]

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[15] Jatkar and Deshpande, *J. Indian Chem. Soc.*, 1960, **37**, 11.

[16] Bunnett and Zahler, *Chem. Rev.*, 1951, **49**, 273.

[17] Bolto and Miller, *Austral. J. Chem.*, 1956, **9**, 74, 304.

[18] Chichibabin, *J. Phys. Chem.* (*U.S.S.R.*), 1914, **46**, 1216.

[19] Chapman and Parker, *J.*, 1951, 3301 and subsequent papers.

[20] Chapman and Russell-Hill, *J.*, 1956, 1563.

[21] Miller and Parker, *Austral. J. Chem.*, 1958, **11**, 302.

[22] Hassan, Karamalla, and Miller, unpublished work.

[23] Brown and Heffernan, *Austral. J. Chem.*, 1956, **9**, 83.

[24] Jaffé, *J. Amer. Chem. Soc.*, 1954, **76**, 3527.

applying the localisation energy method, predicted the order 4, 2 > 3 with 4 slightly more reactive than 2. He also made calculations for the *N*-oxides, pointing out that a static method could not predict enhanced reactivity for both $S_E$ and $S_N$ reactions. By the localisation method, he calculated the order 4 > 2 > 3 for $S_E$ reactions and 4 > 3 > 2 for $S_N$ reactions. The latter agrees neither with our results nor with the experimental work of Ochiai [6] and Colonna and Fattutta; [25] however, Jaffé himself stated that the calculations for the 2-position were unsatisfactory. He also calculated the order: pyridine *N*-oxide > pyridine > benzene.

Our results for methanolysis are actual for the pyridines and pyridine *N*-oxides and computed for the pyridinium compounds from the very similar but slower reaction with *p*-nitrophenoxide ion.[3,8] They are very clear. The 2- and the 4-positions are much more activated than the 3-position, and the effect of the more electronegative nitrogen, corresponding to, but larger than, that of a carbon atom rendered electronegative by an electron-withdrawing substituent, is therefore relayed through $\pi$- as well as $\sigma$-electron systems.

The detailed pattern (Table 2) is of particular interest: (*a*) the enhanced reactivity of the 2- and the 4-position relative to the 3-position is itself in the order pyridinium > pyridine > pyridine *N*-oxides, being about $10^{6-7}$, $10^{3-4}$, $10^{2-3}$, respectively; and (*b*) the

TABLE 2.

Chloropyridine series: ring-atom rate ratios with $OMe^-$–MeOH at 50°.

| Position | Ring atom | | |
|---|---|---|---|
| Cl | N | $N^+–O^-$ | $N^+–Me$ |
| 2 | 1 | $1·93 \times 10^4$ | $4·64 \times 10^{12}$ |
| 3 | 1 | $1·06 \times 10^5$ | $2·87 \times 10^8$ |
| 4 | 1 | $1·12 \times 10^3$ | $5·70 \times 10^9$ |

TABLE 3.

Chloropyridine series: ring-position rate ratios with $OMe^-$–MeOH at 50°.

| Position | Ring atom | | | | | |
|---|---|---|---|---|---|---|
| rel. to Cl | N | | $N^+–O^-$ | | $N^+–Me$ | |
| 2 | $3·02 \times 10^3$ | 1 | $5·52 \times 10^2$ | 1 | $4·89 \times 10^7$ | 1 |
| 3 | 1 | — | 1 | — | 1 | — |
| 4 | * $8·14 \times 10^4$, | † $8·62 \times 10^1$ | * $8·62 \times 10^2$, | † $1·56 \times 10^0$ | * $1·62 \times 10^6$, | † $3·31 \times 10^{-2}$ |

* Conjugative index (C.I.) (Liveris, Lutz, and Miller, *J. Amer. Chem. Soc.*, 1956, **78**, 3375). † Steric index (S.I.) (Miller and Williams, *J.*, 1953, 1475).

TABLE 4.

Chlorobenzene and chloropyridine series: reaction with $OMe^-$–MeOH at 50° (Hammett reaction constant $\rho = 8·47$).

| 2-, 3-, and 4-Cl; C–H | 2-Cl; N | 2-Cl; $N^+–O^-$ | 2-Cl; $N^+–Me$ | 4-Cl; N | 4-Cl; $N^+–O^-$ | 4-Cl; $N^+–Me$ |
|---|---|---|---|---|---|---|
| | $3·31 \times 10^{-8}$ | $6·40 \times 10^{-4}$ | $1·53_5 \times 10^5$ | $8·91 \times 10^{-7}$ | $1·00 \times 10^{-3}$ | $5·08 \times 10^3$ |
| | $2·76 \times 10^8$ | $5·30 \times 10^{12}$ | $1·28 \times 10^{21}$ | $7·43 \times 10^9$ | $8·33 \times 10^{12}$ | $4·23 \times 10^{19}$ |
| | 0·996 | 1·502 | 2·492 | 1·165 | 1·526 | 2·317 |
| $1·20 \times 10^{-16}$ | 3-Cl; N | 3-Cl; $N^+–O^-$ | 3-Cl; $N^+–Me$ | | | |
| 1 | $1·09_5 \times 10^{-11}$ | $1·16 \times 10^{-6}$ | $3·14 \times 10^{-3}$ | | | |
| 0 | $9·12 \times 10^4$ | $9·67 \times 10^9$ | $2·62 \times 10^{13}$ | | | |
| | 0·586 | 1·178 | 1·584 | | | |

Data in order given are: $k_2$ (l. mole$^{-1}$ sec.$^{-1}$), substituent rate factor (S.R.F.), and Hammett substituent constant ($\sigma^*$), respectively, at 50°.

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[25] Colonna and Fattutta, *Gazzetta*, 1953, **83**, 622.

positional order is $4 > 2$ in the pyridines, $4 \approx 2$ in the *N*-oxides, and $4 < 2$ in the pyridinium compounds.

There is a straightforward explanation of the order (*a*). The *N*-oxides activate $S_E$ as well as $S_N$ reactions owing, in the former, to a powerful conjugative (largely electromeric) electron-release by the $O^-$ only partly nullified by the $N^+$ in the ring. In $S_N$ reactions the electron-withdrawal by $N^+$ includes a large electromeric component, but there must still be a residual electron-release by $O^-$ which reduces the reactivity of the 2- and 4- relative to the 3-position, with the observed result.

In an anion–cation reaction there is a reduction in charge on formation of the transition state, resulting in considerable loss of solvation and substantial increase in entropy ($S_{act}$ and $\log_{10} B$). Because of the very powerful activation by ring $N^+$ in the 4-position the resemblance of the transition state to a cyclohexadienide intermediate complex is less than in less activated systems and, as a consequence, in these anion–cation reactions, charge reduction is less. Whereas the residual charges are well separated in the transition state for the 4-pyridinium compound, permitting still substantial solvation of each centre, they are so close in the 2-compound that this is like a normal dipole and there is then simply weak dipole–dipole interaction instead of ion solvation. The result is then order (*b*) above, because the more positive value of $S_{act}$ (high $\log_{10} B$) for reaction of the 2-compound over-compensates the lower value of $E_{act}$ for that of the 4-compound.

The explanation for the *N*-oxides is less obvious and the difference there results from an abnormally low entropy for reaction of the 4-compound, whereas the value for the 2-compound, though a little low also, is nearly normal. It is likely that the negative charge of the cyclohexadienide-type transition state [1,2,16,17] is more concentrated in the *N*-oxides—on oxygen—than it can be in the pyridines, and the former have then relatively large solvation in the transition state and low entropy. Such a difference should be more effective in the 4-compound which is unhindered, whereas in the 2-position the solvation of the partially bonded methoxyl ion and *N*-oxide-oxygen interferes.

The discussion so far leads to the $E_{act}$ order $4 < 2 < 3$ with the reactivity order of 4- and 2-positions modified in each system by entropy considerations in an understandable way.

The relative reactivity of ring substituent: N, $N^+–O^-$, and $N^+$–Me, is shown in Table 3. In the 4-position, $\log_{10}$ rate ratios are *ca.* $1 : 10^3 : 10^9$. The *N*-oxides are not truly intermediate in reactivity; this arises largely because $S_{act}$ is low for the *N*-oxides and high for the pyridinium compounds (see above). The results at the 2-position are similar but made more unusual by the very high $S_{act}$ of methanolysis of the 2-pyridinium compound.

For the 3-position, where transmission is essentially through the $\sigma$-bonds, the situation is rather surprising. After allowance for the increased entropy of methanolysis of the 3-pyridinium compound, and a minor adjustment for the slightly low entropy of the reaction of the 3-chloro-*N*-oxide, the residual reactivity, *i.e.*, that corresponding to $E_{act}$ values, of the $N^+–O^-$ and $N^+$–Me are approximately equal: small differences cannot be considered significant since the pyridinium methanolysis values are obtained from the experimental *p*-nitrophenoxide reactions by calculation. It is not easy to find an uncontroversial explanation for this unexpected result, but we suggest tentatively that the difference in $E_{act}$ of the 3-*N*-oxide and 3-pyridinium compound resulting from the lower electronegativity of nitrogen in the former is counteracted by enhancement of electrostatic stabilisation in its transition state. For both, such stabilisation is expected when neighbouring centres of negative and positive charge are formed. The expected (even if small) $+M$ effect of the formally negative oxygen, which has already been mentioned, could enhance the magnitude of the neighbouring negative charge.

Now that acceptable values of rates and Arrhenius parameters for the methanolysis of chlorobenzene are available,[7] it is possible to consider explicitly the result of substituting ring C–H by N, $N^+–O^-$, or $N^+$–Me. Table 4, constructed from Table 1 with some additional derived data, shows this clearly.

Miller and Wan have calculated the Hammett reaction constant [10] for methanolysis of monosubstituted chlorobenzenes as 8·47 at 50° and, from this and the rates of reaction, Hammett substituent constants ($\sigma^*$) can be calculated for ring substitution;[10] this also allows an intermediate comparison of ring C–H and $C^{\delta+}$ where the $C^{\delta+}$ results from attachment of $-NMe_3^+$.[26]

A Hammett $\rho$ value being known, the $\sigma^*$ value of a substituent can be simply separated into components due to the $E_{act}$ and the $S_{act}$ ($\log_{10} B$) changes. The various pyridine series have only one $\rho$ value, while the value of $\log_{10} B$ and $S_{act}$ quoted for the parent compound (chlorobenzene) is normal for $S_N2$ reactions, so that the separation into two components is justified and useful. The only complication is that at including the 4-chloro-3-nitro-*NNN*-trimethylanilinium salt since kinetic measurements with this (involving $C^{\delta+}$ in the ring) were in a series with a lower $\rho$ value, and we wish, not only to separate the two components of $\sigma^*$ as with the pyridine compounds, but also to interpolate them into the pyridine series. In this respect it must be realised that the entropy contribution seems to be series-invariant, *i.e.*, in both 4-substituted 1-chloro-2-nitrobenzenes and in the pyridine series, despite the difference in $\rho$, the anion–cation reaction raises $S_{act}$ by 15—17 e.u. ($\log_{10} B \sim 3{\cdot}5$). Thus, after separation of the two components of the $\sigma^*$ value of *p*-$NMe_3^+$, the entropy component has been converted back into the equivalent part $-\sigma^*$ for the $\rho$ value of the pyridine series, giving the total $\sigma^*$ value 0·647 as against the original value 1·110;[26] numerically, 0·251 + 0·859 becomes 0·251 + 0·396 for the $\rho$ values 3·90 and 8·47, respectively.

For the 4-position, the $\sigma^*$ values (with interpolation of $C^{\delta+}$ between CH and N) are then 0, 0·647, 1·165, 1·526, and 2·317. After allowance for the enhanced entropy contribution to the pyridinium and anilinium compounds and reduced entropy for the *N*-oxide, the values could be modified as explained to 0, 0·251, 1·165, 1·674, and 2·164. Jaffé [24] suggests $\sigma^*$ values for the 4-*N* and 4-*N*-oxide of 0·93 and 1·88, respectively. Entropy effects in the pyridine are negligible.

Though $\sigma^*$ values can be computed for aromatic substitutions in the 2-position they are normally less widely applicable because of substantial and varying steric effects; however, in the present case we are dealing with ring substitution and this is much less of a problem (the anilinium compound is an exception but results for it too are included for interest). These values are similarly $\sigma^* = 0$, 0·762,[27] 0·996, 1·502, and 2·492, but modified as explained above to 0, 0·436, 0·878, 1·567, and 2·079. Jaffé's [24] value of $\sigma^*$ for 2-*N* is 0·81. From the values of $E_{act}$ it is seen that activation from the 2-position in the pyridines is about 75% and in the other two series about 95%, of that from the 4-position (cf. refs. 9, 24, and 28).

For the 3-position, where $\sigma$-bond relay controls the situation, values are 0, —, 0·586, 1·178, and 1·584 and may be modified as explained above to 0, —, 0·596, 1·225, and 1·147; but here the difference between 1·225 and 1·147 is too small to be significant since the latter is a calculated value from *p*-nitrophenoxide reactions. The approximate equality of *N*-oxide and pyridinium compound as regards $E_{act}$ has been discussed above. Jaffé [24] suggests $\sigma^*$ values for the 3-*N* and 3-*N*-oxide of 0·62 and 1·59, respectively.

The results of replacing ring atoms are enormous, so that some of the corresponding $\rho$ values are the largest so far recorded. It should be possible to correlate this reactivity change with some quantity representing the electronegativity difference of benzene-carbon and the replacing atom. This would be to some extent speculative, and subject to considerable error, yet the conclusions could be of interest.

Pauling's electronegativity indices [29] or the effective nuclear charge may be suitable for this purpose. The former are 2·5 for carbon and 3·0 for nitrogen, but refer to states

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[26] Daly, Kruger, and Miller, *Austral. J. Chem.*, 1958, **11**, 290.

[27] Bolto and Miller, unpublished work; $\rho$ is assumed to be as in 1-chloro-2-nitro-4-*X*-benzenes.

[28] Miller and Williams, *J.*, 1953, 1475; Bunnett and Morath, *J. Amer. Chem. Soc.*, 1955, **77**, 5051, 5165; Parker and Read, *J.*, 1962, 3149.

[29] Pauling, " The Nature of the Chemical Bond," 3rd edn., Cornell Univ. Press, Ithaca, N.Y., 1960, p. 93.

of $sp^3$-hybridisation[30] and should be larger for $sp^2$ and still larger for $sp$-states. For $sp$-carbon a value of 3·1 has been given,[31] from which values for $sp^2$-carbon and nitrogen of 2·8 and 3·3 may be estimated. Relating modified $\sigma^*$ values (*i.e.*, those based on $E_{act}$ values alone) to these two, the following electronegativity indices of the ring substituents may be estimated: C(–H), 2·8; $C^{\delta+}$ ($-NMe_3^+$), $2{\cdot}9_1$; N, 3·3; $N^+(-O^-)$, $3{\cdot}5_2$; and $N^+$(–Me), $3{\cdot}8_3$.

From the difference $sp^2 - sp^3$ estimated above the value of the index for nitrogen of $-NMe_3^+$ is $3{\cdot}5_3$, so that it raises that of the benzene-carbon by 0·11/0·73 of the difference in indices (15% or about $\frac{1}{7}$th). This may be compared with the relationship of auxiliary inductive parameters to Coulomb integrals,[32a] for which a ratio of 1 : 10 is commonly adopted but for which values 1 : 3 to 1 : 8 have also been used.[32b]

In view of the comment on some heterocyclic systems by Bassett and Brown,[33] it is worth extending this approximate correlation to ring-$N^-$ by assuming the same change from $N^-$ to N as for N to $N^+$. We would then estimate indices for ring-$N^-$ as $2{\cdot}7_7$ and $2{\cdot}4_7$ when using $sp^2$- and $sp^3$-hybridisation, respectively, *i.e.*, values approximately equal to these of corresponding electrically neutral carbon.

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[30] Ingold, " Structure and Mechanism in Organic Chemistry," G. Bell and Sons Ltd., London, 1953, p. 174.

[31] Heel and Zeit, *Z. Elektrochem.*, 1960, **64**, 962.

[32] Streitweiser, " Molecular Orbital Theory for Organic Chemists," Wiley and Sons, New York, 1961, (*a*), p. 118, (*b*) p. 128.

[33] Bassett and Brown, *J.*, 1954, 2701 and subsequent papers.