Determination of a New Scale of *ortho*-Steric Parameters S^0 from *N*-Methylation of Pyridines

By **Ulf Berg,** Organisk Kemi 1, Kemi Centrum, Box 740, S22007 Lund 7, Sweden
Roger Gallo,* Gerd Klatte, and **Jacques Metzger,** I.P.S.O.I., Faculte des Sciences et Techniques, St. Jerome, 13013 Marseille, France

The kinetics of quaternisation by methyl iodide of 33 substituted pyridines was measured in acetonitrile at 30 °C; the reactions were followed by n.m.r. with a competitive technique. The relative rate constants were similar to those observed in other polar aprotic solvents. Steric effects exist for all the *ortho*-substituents and can be estimated from the deviation from the Brønsted plot. A scale of *ortho*-steric parameters (S^0) is proposed. There is no significant dependance of S^0 on the Dougard–Decroocq solvent parameters and a complete lack of correlation between S^0 and the electronic effects of substituents. The relative S^0 values agree with other experimental estimations of the steric size of substituents. The S^0 parameters are discussed in terms of substituent structure in connection with the Taft–Kutter–Hansch E_s and Charton υ parameters. The general applicability of a unique scale of steric parameters is discussed.

STERIC effects are important in the structure and reactivity of organic molecules. An understanding of their influence comes from quantitative estimations made using linear free energy relationships.[1-5] For aliphatic molecules Taft originally proposed a scale of parameters E_s derived from the rate constants in acid catalysed hydrolysis of esters [1] [equation (1)]. Charton

$$\log k/k_0 = E_s \qquad (1)$$

has demonstrated their validity and shown that they are linearly correlated to the van der Waals radii.[6] Despite some minor criticisms,[7-9] the E_s parameters, or their corrected values are widely used.[1-5]

For aromatic compounds several scales of *ortho*-steric parameters have been proposed, by Taft (E_s^0),[1] by Farthing and Nam (σ_s),[10] by Kindler,[11] and by Hussey and Diefendorfer (S.F.).[12] From a statistical analysis Charton concluded [5] that these parameters are independent of the size of the substituents † and are in fact electrical effect parameters.

We propose a new scale for *ortho*-steric effects based upon results of quaternisation of pyridines where the steric and electronic effects of *ortho*-substituents can be separated. We would like to analyse these results and to discuss the general applicability of a unique scale of steric effects.

RESULTS AND DISCUSSION

The relative rate constants for the quaternisation of 33 substituted pyridines with methyl iodide in acetonitrile are given in Table 1. The kinetics were determined at 30 °C by n.m.r. according to the competitive technique described by Deady and Zoltewicz; [13] suitable standards were used depending upon the reactivity of each compound studied.

The reactivity covers a range of 10^4. All *ortho*-substituted pyridines (14)—(33) are less reactive than the unsubstituted parent compound. The relative rates measured in acetonitrile are in good agreement with those found for *N*-methylation of 2-alkylpyridines in nitrobenzene,[14] and for *N*-methylation of 2-substituted pyridines in DMSO.[13]

The effect of *ortho*-alkyl substituents on quaternisation of pyridines was recognized long ago to be steric in character; [15] for other *ortho* substituents, Deady and Zoltewicz [13] showed that electronic effects are superimposed on steric effects and that the steric effects are nearly the same for NH_2, Me, Cl, Br, and CN, but are

TABLE 1

Relative rate constants for *N*-methylation of substituted pyridines by methyl iodide in acetonitrile at 30 °C

Compd.	Substituent	k/k_H	$\log k/k_H$	Ref.	pK_a [e]
(1)	H	1.00	0	*a*	5.19
(2)	4-NH_2	17.1	1.23	*a*	9.11
(3)	3,4-Me_2	4.23	0.626	*b*	6.50
(4)	3-NH_2	4.01	0.603	*b*	6.00
(5)	3,5-Me_2	3.97	0.599	*b*	6.20
(6)	4-Me	2.22	0.346	*b*	6.00
(7)	3-Me	2.08	0.318	*b*	5.68
(8)	3-COMe	0.407	−0.390	*a*	3.18
(9)	3-$CONH_2$	0.375	−0.426	*b*	3.28
(10)	4-COMe	0.343	−0.465	*a*	3.51
(11)	3-Br	0.100	−1.00	*b*	2.84
(12)	4-CN	0.096	−1.02	*a*	1.86
(13)	3-Cl	0.090	−1.05	*a*	2.94
(14)	2-Me	0.50	−0.30	*a*	5.96
(15)	2-Et	0.19	−0.72	*a*	5.89
(16)	2-Pr^i	0.080	−1.10	*a*	5.83
(17)	2-Bu^t	0.000 20	−3.70	*a*	5.76
(18)	2-CH_2Ph	0.089	−1.05	*a*	5.13
(19)	2-Ph	0.010	−2.00	*a*	4.77
(20)	2-CH_2OH	0.26	−0.59	*a*	4.86
(21)	2-CH_2CH_2OH	0.21	−0.68	*a*	5.31
(22)	2-Br	0.0044	−2.36	*a*	0.71
(23)	2-CN	0.0020	−2.70	*a*	−0.26
(24)	2-OPh	0.0094		*a*	
(25)	2-NH_2	0.50	−0.30	*a*	6.86
(26)	2-NMe_2	*c*	−1.6	*a*	6.99
(27)	2-(2-Pyridyl) [d]	0.0033	−2.48	*a*	4.48
(28)	2-CHO	0.0023	−2.64	*a*	3.77
(29)	2-COMe	0.000 91	−3.04	*a*	2.64
(30)	2-CO_2Et	2.0072		*a*	
(31)	2-COPh	0.0054		*a*	
(32)	2-(*p*-ClC_6H_4CO)	0.0033		*a*	
(33)	2-(1-Pyrrolyl)	0.000 51		*a*	

[a] This study. [b] From U. Berg, R. Gallo, and J. Metzger, *J. Org. Chem.*, 1976, **41**, 2621. [c] *exo*-Nitrogen methylation 95%. [d] Statistically corrected for two equivalent nitrogen atoms. [e] From D. D. Perrin, ' Dissociation Constants of Organic Bases in Aqueous Solution,' Butterworths, London, 1965.

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† Except perhaps the S.F. parameters.

more important for Et, CH_2Ph, 2-pyridyl, CO_2Me, and NHCOMe. More recently Seydel *et al.* showed that the steric and electronic effects of *ortho*-substituents are similar for both quaternisation and antibacterial activity in pyridines.[16]

In order to evaluate quantitatively the steric contribution of each *ortho*-substituent to the $\Delta G^{\ddagger}$ value of the reaction we assumed that the electronic and steric effects can be separated. The electronic effects of the substituents can be estimated by the two dual parameter equations (2) and (3). However, these equations have

$$ortho\text{-electronic effect} = \lambda\sigma_I + \delta\sigma_R \quad (2)$$

[17]

$$ortho\text{-electronic effect} = \rho\sigma_p + f\mathrm{F} \quad (3)$$

[3]

some limitations: the ratio $\varepsilon = \delta/\lambda$ varies for the *ortho*-, *meta*-, and *para*-positions[5] and the simplification of using σ_p for the *ortho* position is not fully established for the pyridine series.[18,19]

A more straightforward possibility is the use of pK_a values since they include both polar, resonance, and field effects, and are accessible for *ortho*- as well as *meta*- and *para*-positions. Furthermore pK_a values and proton affinities in the gas phase are not appreciably influenced by the steric requirements of the *ortho*-substituents[13,20-22] apart from very strongly hindered bases such as 2,6-di-t-butylpyridine.[23-25] The parameters of the Brønsted relation (4) determined with reactivity and basicity data

$$\log k/k_{\mathrm{H}} = \alpha pK_a + c \quad (4)$$

for compounds (1)—(13) (Table 1) are α 0.350,[*] c —1.73, and R 0.967.

All the *ortho*-substituents plotted in Figure 1 fall below the Brønsted line, indicating a reactivity lower than that expected from pure electronic effects. Steric effects exist for each *ortho*-substituent and can be calculated according to equation (5). This procedure was repeated

$$S^0 = \log k/k_{\mathrm{H}} - (\alpha pK_a + c) \quad (5)$$

to obtain new values for other substituents from available data of quaternisation of pyridines determined in DMSO,[13] $PhNO_2$,[14,22] sulpholan,[26] and acetone[27] (Table 2). Several S_i^0 values for the same substituent were therefore obtained when this substituent was studied in different solvents.

When compared, the individual and the mean value of S^0 for each substituent do not differ by more than 0.10 (which is an acceptable error for l.f.e.r.s)[28] except for CH_2OH, Br, CN, CHO, NH_2, and NHAc. These differences can come from errors in the determination of the Brønsted slope,[†] from specific interactions and ambident reactivity (*e.g.* aminopyridines), or from a dependence of the S^0 values with the solvent. It seemed reasonable, therefore, to test this hypothesis by plotting the individual S_i^0 parameters available for a given solvent (Table 2) *versus* the mean $\bar{S}^0$ values obtained from results in several solvents, according to equation (6).

$$S_i^0 = \beta\overline{S^0} \quad (6)$$

The slopes of the correlations obtained for each solvent are: DMSO, $\beta = 1.01 \pm 0.07$; $PhNO_2$, $\beta = 0.95 \pm 0.03$; MeCN, $\beta = 0.98 \pm 0.016$; acetone, $\beta = 1.01 \pm 0.05$. These results suggest a very small dependence (at the limit of significance) of *ortho* steric effects with the solvent. When the parameters just determined are plotted against the solvent parameter[‡] of Drougard and Decroocq[30] [equation (7)] the slope of the correlation

$$\beta = sS \quad (7)$$

$s = 0.5 \pm 8.7$ ($R = 0.03$) is not significant. It follows that there is a very small variation (if any) of steric parameters S^0 for *N*-methylation of pyridines in polar aprotic solvents. These results are in agreement with the accepted small solvent dependence of the *relative* rate constants of quaternisation reactions,[17,31] and with the quasi-invariance of the isomer ratio observed in quaternisation of diazines in numerous aprotic solvents.[32]

The parameters S^0, expressed as $\Delta\Delta G^{\ddagger}/2.303RT$ are reported in Table 3. The value $S^0 = 0$ corresponds to the hydrogen atom. Depending on whether only steric or both steric and electronic effects operate equations (8) and (9) should be used respectively.

$$\log k/k_{\mathrm{H}} = \delta S^0 \quad (8)$$

$$\log k/k_{\mathrm{H}} = \delta S^0 + \rho_I\sigma_I + \rho_R\sigma_R \quad (9)$$

It is now necessary to test the validity of this new scale of *ortho*-steric parameters. The first point concerns the nature of the S^0 constants. The main objection to the steric scales already reported is that they are in part, if not completely, a measure of electronic effects.[5,7,8] To test this possibility we correlated the S^0 constants with the electronic effects of the substituents expressed by the pK_a of the corresponding *ortho*-pyridines. The complete lack of correlation ($R = 0.15$) clearly indicates that if there is no significant electronic contribution to S^0, it statistically vanishes over the whole set of substituents considered.

We have also compared the S^0 constants with other experimental measures of the steric size of substituents. The S^0 parameters for the substituents Me, Et, Pr^i, and Bu^t follow the usual exponential increase of bulk for this series; the S^0 parameters correlate linearly with steric energies for 2-methyl-, 2-ethyl-, 2-isopropyl-, and 2-t-butyl-pyridinium ions as calculated by the empirical force field method.[33,34] The value for methyl compared

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[*] The slope of this Brønsted relation is very similar to those observed for quaternisations of other pyridine derivatives in $PhNO_2$,[14,22] $MeNO_2$,[20] and DMSO[13] (all the α values fall in the range $0.35 < \alpha < 0.43$).

[†] It should be noted that the consequences of error in the slope and intercept of the Brønsted plot are most serious for the ($\alpha pK_a + c$) component of S^0 for substituents lying towards the ends of the Brønsted line, *e.g.* Br, NH_2, and CN.

[‡] A recent study of Auriel and de Hofmann showed that the solvent parameter of Drougard and Decroocq constitutes a more comprehensive measure than any other physical characteristic.[29]

TABLE 2

log k/k_H and S_i^0 values of *ortho*-steric effects [a] for quaternisation of *ortho*-pyridines by methyl iodide

ortho-Substituent	Acetonitrile [b]	Nitrobenzene [c]	DMSO [d]	Sulpholan [e]	Acetone [f]	Mean S^0 values	pK_a [g]
H	0	0	0	0	0	0	5.19
Me	−0.30 (−0.66)	−0.32 (−0.70)	−0.42 (−0.84)		−0.42 (−0.70)	−0.73	5.96
Et	−0.72 (−1.06)	−0.66 (−1.01)	−0.77 (−1.17)			−1.08	5.89
Pr^i	−1.10 (−1.41)	−1.14 (−1.46)				−1.44	5.83
Bu^t	−3.70 (−3.99)	−3.60 (−3.89)				−3.94	5.76
CH_2Ph	−1.05 (−1.12)		−1.09 (−1.19)			−1.16	5.13
CH_2OH	−0.59 (−0.57)				−0.88 (−0.77)	−0.67	4.86
CH_2CH_2OH	−0.68 (−0.81)				−0.85 (−0.90)	−0.86	5.31
Cl		−2.22 (−0.23) [h]	−2.41 (−0.70)		−2.37 (−0.68)	−0.54	0.49
Br	−2.36 (−0.88)	−2.49 (−0.60)	−2.41 (−0.79)		−2.62 (−1.01)	−0.82	0.71
CN	−2.70 (−0.88)		−2.66 (−0.66)		−3.09 (−1.14)	−0.89	−0.26
NH_2	−0.30 (−0.98)		+0.09 (−0.87)			−0.93	6.86
NHAc			−2.09 (−1.79)		−2.46 (−2.07)	−1.93	4.09
NMe_2	−1.60 (−2.32)					−2.32	6.99
OMe					−1.96 (−1.28)	−1.28	3.28
OEt					−2.00 (−1.36)	−1.36	3.40
$CH=CH_2$					−1.55 (−1.48)	−1.48	4.98
CHO	−2.64 (−2.23)				−2.99 (−2.48)	−2.36	3.77
COMe	−3.04 (−2.24)					−2.24	2.64
CO_2Me			−2.08 (−1.04)			−1.04	2.22
CO_2Et	−2.14 (−1.25)					−1.25	2.46
Ph	−2.00 (−1.94)			−1.96 (−1.81)	−1.86 (−1.71)	−1.82	4.77
2-Tolyl				−0.89 (−0.77)		−0.77	4.83
Mesityl				−0.27 (−0.23)		−0.23	5.06
4-Methoxyphenyl				−1.89 (−1.82)		−1.82	4.99
4-Nitrophenyl				−2.70 (−2.18)		−2.18	3.70
2-Thienyl				−2.96 (−2.46)		−2.46	3.76
3-Methyl-2-thienyl				−2.14 (−1.75)		−1.75	4.06
1-Naphthyl				−0.96 (−0.75)		−0.75	4.57
2-Pyridyl	−2.48 (−2.32)		−2.53 (−2.38)			−2.35	4.48

[a] The individual determinations of S_i^0 are from the equation $S_i^0 = \log k/k_H - (\alpha pK_a + c)$; the solvent parameters (α and c) used are: acetone, α 0.36, c −1.86;[27] DMSO, α 0.39, c −1.90;[48] sulpholan, α 0.35, c −1.81; nitrobenzene, α 0.43, c −2.20; acetonitrile, α 0.35, c −1.73. The values for nitrobenzene and acetonitrile were calculated from the Brønsted relation $\log k/k_H = \alpha pK_a + c$ using a least-squares treatment. For nitrobenzene the log k/k_H values of refs. 14 and 22 were used. [b] Data from this study. [c] From ref. 14. [d] From ref. 13. [e] From ref. 26. [f] From ref. 27. [g] From D. D. Perrin, 'Dissociation Constants of Organic Bases in Aqueous Solution,' Butterworths, London, 1956. [h] log k/k_H values from ref. 22.

to those for Cl and Br agrees with the values for the effective size of the substituents deduced from dynamic stereochemistry studies.[35-37] While the unsubstituted NH_2 has almost the same size as methyl, the large increase of S^0 values ($NH_2 < NHAc < NMe_2$) is in agreement with the relative ratio of isomers formed in alkylation of pyridazines.[38] The steric requirements of planar aromatic and heteroaromatic groups depend upon the angle of twist between the ring and the substituent. Thus phenyl has almost the same size as isopropyl, while mesityl is smaller than methyl; this is in agreement with the relative van der Waals radii of methyl and the half-thickness of the π-cloud of the aromatic ring.[39] According to this methyl is almost as large as naphthyl; however, 2-pyridyl and 2-thienyl can accommodate more coplanar structures and hence have larger S^0 values.

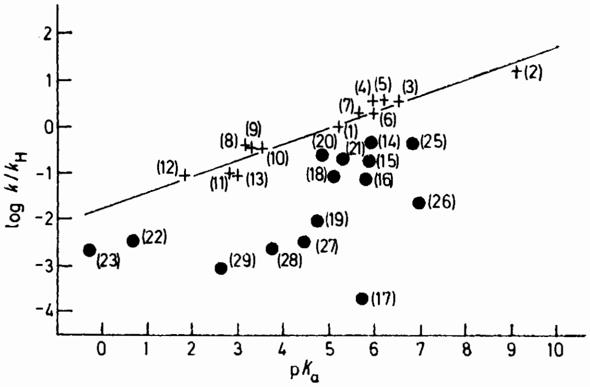


FIGURE 1 Relative rate constants for alkylation of pyridines by methyl iodide in acetonitrile at 30 °C *versus* pK_a of the corresponding pyridines. For key see Table 1

The next question which arises is whether the S^0 parameter is really different from other already existing scales, *i.e.* is a new scale of steric effects necessary? To investigate this point we have correlated S^0 with the E_s^c constants of the Taft–Kutter–Hansch extended scale,[4] by far the most widely used. The correlation is very poor and substituents fall on different lines (Figure 2).

TABLE 3

S^0 parameters of *ortho*-steric effect

Substituent	S^0	Substituent	S^0
H	0	$CH{=}CH_2$	−1.48
Me	−0.73	CHO	−2.36
Et	−1.08	COMe	−2.28
Pr^i	−1.44	CO_2Me	−1.04
Bu^t	−3.94	CO_2Et	−1.25
CH_2Ph	−1.16	Ph	−1.82
CH_2OH	−0.67	2-Tolyl	−0.77
CH_2CH_2OH	−0.86	Mesityl	−0.23
Cl	−0.54	4-Methoxyphenyl	−1.82
Br	−0.82	4-Nitrophenyl	−2.18
CN	−0.89	2-Thienyl	−2.46
NH_2	−0.93	3-Methyl-2-thienyl	−1.75
NHAc	−1.93	1-Naphthyl	−0.75
NMe_2	−2.32	2-Pyridyl	−2.35
OMe	−1.28		
OEt	−1.36		

The discrepancy observed when correlating reactivity data with E_s constants has been attributed, at times, to the contribution of hyperconjugative effects to E_s.[7,8] Corrected E_s parameters thus proposed (E_s^c of Hancock and E_s^0 of Palm) were regarded with some scepticism by Shorter;[2] Charton[40] and Dubois[41] did not find any statistical improvement in their use. We included E_s^c and E_s^0 in the correlation with S^0 and did not observe any significant change in the general trend. Recently Charton and Dubois, respectively, have proposed new steric parameters υ[40,42] and E_s'.[9,41] The E_s' values are specially suited for highly congested groups which we have not investigated. The υ parameters were proposed by Charton after a statistical analysis of steric effects; a limited basic set of symmetrical substituents was defined from van der Waals radii, but all additional υ values come from kinetic data for ester hydrolysis and carboxylic acid esterification (the reference reactions used by Taft to define E_s). As expected the correlation between S^0 and υ shows the same discrepancy as for E_s.

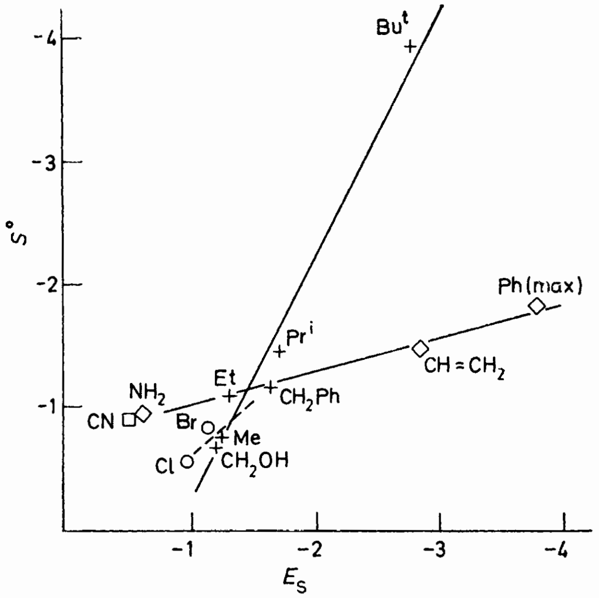
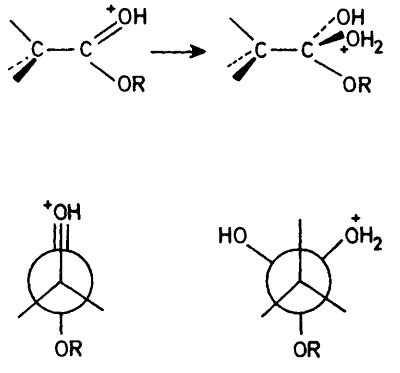


FIGURE 2 S^0 *ortho*-parameters *versus* E_s^e extended Taft–Kutter–Hansch steric parameters

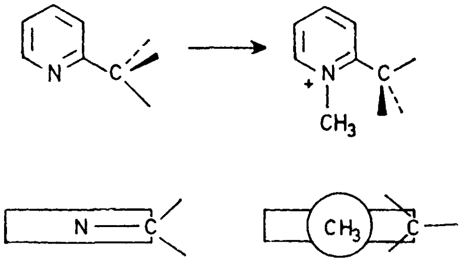
The modifications of the original E_s scale have been designed to achieve a better separation of electronic and steric effects. While these studies are important in correctly defining parameters under given conditions, the decisive point, in our opinion, is the precise delineation of the scope and limitations of any unique scale of steric parameters. Some time ago we proposed a limitation on the applicability of the Taft E_s parameters when the free rotation of alkyl groups was prevented.[43] Other authors have also stressed the importance of conformation in quantitative studies of steric effects.[2,4,9,44-47]

By representing the ground and transition states of the acid catalysed hydrolysis of esters (Scheme 1) and of the quaternisation of pyridines by a methylating agent (Scheme 2) it is possible to understand better the differences which arise between S^0 and E_s. A glance at the Newman projection in Schemes 1 and 2 show that the E_s

values arise from interactions between a substituent and three groups bonded to a tetrahedral carbon, whereas S^0 is derived from interactions between a substituent and one adjacent group. Another point to be taken into account is the division of the substituents into three main classes depending on their symmetry. The first class contains spherical or cylindrical substituents, *e.g.* Cl, Br, Me, and CN. The second class contains tetrahedral substituents where the atom bonded to the rest of the molecule is sp^3 hybridised, *e.g.* alkyl groups. The third class contains planar substituents bonded by an sp^2 atom, *e.g.* COMe, CO_2R, $CH{=}CH_2$, Ph, and heteroaryl. The following observations can be made even if the number of values in each series is limited.



Scheme 1



Scheme 2

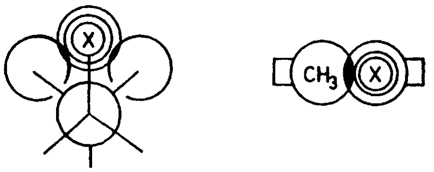
For spherical substituents (Cl, Br, Me) a correlation exist ($\alpha = 1$) between E_s and S^0 (Scheme 3).*

For tetrahedral substituents two situations must be considered, substitution at the α-carbon, *e.g.* the α series of Ingold (Me, Et, Pr^i, and Bu^t) and substitution at the β-carbon *e.g.* Et, CH_2Ph, and CH_2R. For the α-series steric interactions increase sharply in both cases, and the most substituted group (Bu^t) suffers steric hindrance in the *gauche*-conformations in the two reference reactions (Scheme 4a). For the β-substituted groups CH_2R on the other hand, *gauche*-interactions exist for all substituents in the tetrahedral intermediate of the acid catalysed hydrolysis of esters (Scheme 4b), whereas a CH_2R group can rotate to adopt a much less bulky conformation in the quaternisation of pyridines. Therefore the α- and β-series have completely different behaviours and fall on two distinct lines (slopes 1.8 and 0.2).†

For planar substituents no definitive conclusion can be drawn since only two values could be compared ($CH{:}CH_2$ and Ph); however they fall on the line parallel to that of the CH_2R substituents.

The above discussion shows that good correlations can be observed for substituents with the same symmetry, but there is no reason, *a priori*, to obtain linear relations between groups of different symmetry when conformational preferences of a different nature exist such as in aliphatic and heteroaromatic molecules. We can therefore state that a unique single parameter scale of steric effects is not applicable to both aliphatic and heteroaromatic series.

There are at present two alternatives to that situation.

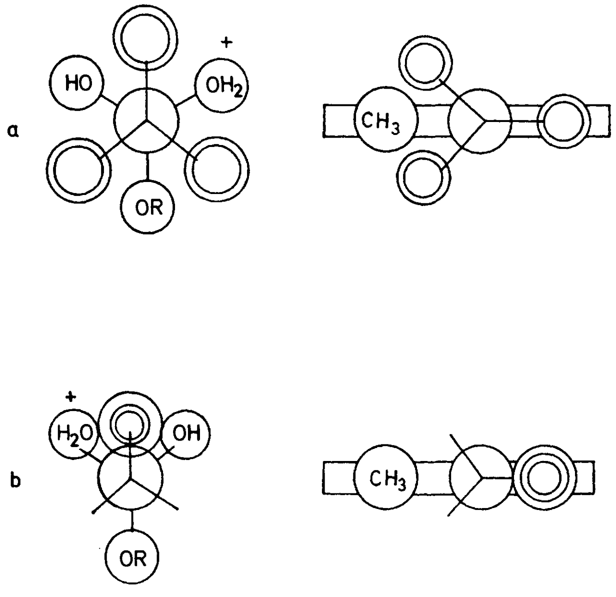


Scheme 3

The first is that several values of the steric constants could be proposed for the same substituent by factoring into a linear combination of subfragments (*cf.* ref. 44), *e.g.* equation (10), or by selecting a value among a set of

$$E_s(C_{XYZ}) = aE_s(X) + bE_s(Y) + cE_s(Z) + d \quad (10)$$

five calculated constants for the same substituent (*cf.* ref. 47). The two methods are however limited by the need to assume preferred conformations or to use very large sets of compounds to be statistically meaningful.



Scheme 4

The other alternative is the use of different steric

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* The E_s values of Cl and Br were determined for the series CH_2X since the methyl substituent is the reference group.

† The same behaviour has also been reported very recently by Schaper in a quantitative study of methylation of pyridine derivatives.[48] Moreover the α- and β-series of Ingold (β series, Et, Pr^n, Bu^i, neopentyl) have been studied for the quaternisation of 2-substituted thiazoles [49] and follow the trend in Figure 2.

scales for different molecular structures. To correlate properties of aliphatic molecules nothing basically different has been proposed apart from the E_s scale or its related forms, E_s^0, E_s^c, E_s^e, υ, E_s', and E_s^*.[4,7-9,40,42,50] The conditions for choosing the appropriate scale and a more precise delineation of its use is however needed. For heteroaromatic molecules, which form a majority in QSAR studies, we propose to use the S^0 parameters. Molecular mechanics calculations, presently underway, will help to put the S^0 parameters on a correct energy basis.[33] In a later paper we shall extend and apply the S^0 scale.

EXPERIMENTAL

Materials.—All pyridines were commercially available. They were purified by fractional distillation or crystallization and in some cases by repeated crystallization of the hydroperchlorate salt. Purity was checked by g.l.c. Acetonitrile was purified by distillation after treatment by anhydrous sodium carbonate and kept over molecular sieves. Methyl iodide was distilled over mercury and stored at −16 °C over mercury.

Relative Rate Determinations.—The relative rates of methylation with methyl iodide were determined by n.m.r. by the competitive technique previously described by Lund [38] and by Deady and Zoltewicz.[13] The 2-substituted pyridine (1—1.5 mmol) and a suitable standard (1—1.5 mmol) were weighed into a glass tube and acetonitrile (2 ml) and methyl iodide (0.4 mmol, 60 mg) were added. After shaking, the tube was allowed to stand at 30 °C until all the methyl iodide was consumed. For the less reactive pyridines an excess of methyl iodide was used and the reaction mixture was analysed after *ca.* 25% conversion. The solvent was evaporated *in vacuo*, and the residue dissolved in either deuteriated dimethyl sulphoxide (0.7 ml) or trifluoroacetic acid (0.7 ml).

The rate data are mean values of 2—4, usually 3, experiments, with a reproducibility of 10% for the relative rate constants. The rate constant ratio k_1/k_2 was calculated from the concentrations of the competing heterocycles, initially and after a given time t using equation (11). The

$$k_1/k_2 = \frac{\log[\mathrm{het}_1]_t/[\mathrm{het}_1]_0}{\log[\mathrm{het}_2]_t/[\mathrm{het}_2]_0} \qquad (11)$$

rate constant ratios determined at various stages of the reaction (20—40%) agree within 10%. More than one competitive standard was used for each pyridine and the agreement between each cross experiment was 10%. For 4-aminopyridine, however, the reproducibility was only 30% depending upon the reference standard. The n.m.r. spectra were recorded on Perkin-Elmer R-32, JEOL HM-100, or Varian EM-360 spectrometers.

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