Differentiation of Substituent Effects from Hydrogen Bonding and Protonation Effects in Carbon-13 NMR Spectra of Pyridine *N*-Oxides

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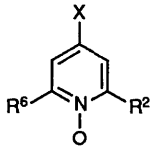
Aromatic ^{13}C chemical shifts are reported for 4-substituted and 3-substituted pyridine *N*-oxides measured in deuteriochloroform, deuterium oxide, perchloric acid (60% in D_2O) and dichloroacetic acid (80% in $CDCl_3$), and also for *O*-alkylated derivatives in $(CD_3)SO$ and D_2O. The substituent chemical shift (SCS) data show systematic non-additivity in comparison with monosubstituted benzenes. Data for the position *para* to the variable substituent were analysed by means of the dual substituent parameter equation. For this position multiple substituent interactions are responsible for the non-additive shifts; interactions have both an inductive (polar) and a resonance component. Hydrogen bonding and protonation effects were differentiated from the substituent effect. It is shown that the relative ^{13}C chemical-shift difference $[(\Delta_3 - \Delta_4)/\Delta_3]$ is a measure of the hydrogen bond and protonation effects and is not subject to substituent effects. 3-Dimethylaminopyridine *N*-oxide is protonated at the dimethylamino group, but 4-dimethylaminopyridine *N*-oxide at the oxygen.

Heterocyclic amine *N*-oxides are compounds of interest, owing to their biological activity.[1,2] Relatively few aromatic *N*-oxides occur in nature, but a large number of them have been synthesized and tested for biological activity.[3] The oxidation of several heterocyclic amines lead to formation of the *N*-oxides as metabolites. The heteroaromatic amino group is very common in drug molecules and recent studies with pyridine model compounds suggest that oxidation at this type of nitrogen may quantitatively be an important route of metabolism *in vivo*.[4]

Hydrogen-bonding associations have often been invoked in biological process, *e.g.* anaesthetic potency,[5,6] sugar transport[7] or anti-tumour activity.[8] Therefore pyridine *N*-oxide and its derivatives are particularly interesting from the point of view of substituent and hydrogen bonding effects.

Empirical models based on the additivity of fixed increments have proved, in the past, to be very powerful in the elucidation of ^{13}C spectra in organic structural analysis.[9] More recent studies,[10–13] suggest that strict additivity does not always apply, *e.g.* in disubstituted benzenes.

In this paper we report accurate substituent chemical-shift (SCS) data for a series of 4- and 3-substituted pyridine *N*-oxides,



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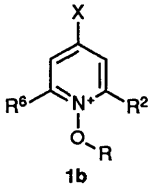

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(**1**, **2**) their protonated and *O*-alkylated derivatives and the differentiation of the substituent effects from hydrogen bonding and protonation effects. We have examined the non-additivity at the *ipso*-, *ortho*- and *para*-positions, of substituent variation in order to obtain insight into substituent–substituent interactions. Furthermore, recent work has highlighted the importance of ^{13}C parameters, and particularly of protonation shifts in the study of the hydrogen bonding.

Experimental

All spectra were recorded on a JEOL FX-90Q spectrometer at 25.1 MHz with a ^2H lock. Typical conditions were spectral width 5000 Hz, 8K data points, pulse width 9 μs. These conditions resulted in a digital resolution of 1.22 Hz (*i.e.* 0.05 ppm). All spectra were proton–noise decoupled. Sample concentrations were 0.3 mol dm^{-3} except for 4-cyanopyridine *N*-oxide in $CDCl_3$ and 4-nitro derivatives in D_2O and 60% $HClO_4$, which were run as saturated solutions (*ca.* 0.01 mol dm^{-3}).† The centres of the peaks of $CDCl_3$ (77.11 ppm), $(CD_3)_2SO$ (39.5 ppm) and dioxane 67.35 ppm) were used as internal references.

Substituted pyridine *N*-oxides,[14] OMe,[15] and OCH_2Ph[16] derivatives were prepared as described. All gave satisfactory C, H and N analyses. Perchloric acid (60%) was prepared by mixing 72% acid with D_2O. Dichloroacetic acid (DCA) (80%) was prepared by mixing the acid with $CDCl_3$. Deuteriochloroform was stored over molecular sieves 4 Å, and $(CD_3)_2SO$ was dried by distillation. All samples were protected from moisture.

† The chemical shifts vary with concentration and values of secondary reference shift and may be affected by instrumental factors. All organic solvents contain traces of water and the sample:water ratio increases with dilution. Variation of the chemical shifts with concentration in organic solvents may be due to hydration, [see, *e.g.*, Z. Dega-Szafran, M. Szafran and J. Rychlewski, *J. Chem. Soc., Perkin Trans. 2*, 1978, 536]. Another contribution to the concentration effect on the chemical shift may be an aggregation (dipolar association) [see, *e.g.*, *Aggregation Processes in Solution*, ed. E. Wyn-Jones and J. Gormally, Elsevier, Amsterdam, 1983]. Pyridine *N*-oxides and their complexes with acetic acids, as do other dipolar molecules, form aggregates in low polar solvents ($nB = kB_m$; $nHA + mB = m(AHB) + k(AHB)_1$) [see, *e.g.*, M. Grundwald, M. Szafran and M. Kreglewski, *Adv. Mol. Relax. Interact. Processes*, 1980, **18**, 53; Z. Dega-Szafran, M. Szafran and M. Kreglewski, *J. Chem. Soc., Perkin Trans. 2*, 1980, 1516]. Both the downfield and upfield ^{13}C shifts were observed as a function of concentration [see, *e.g.*, H. Saito, Y. Tanaka, S. Nagata and K. Nukada, *Can. J. Chem.*, 1973, **51**, 2118]. To compare our results with the previous ^1H NMR and IR data we used the same concentration and protected samples from moisture.

Table 1 ^{13}C SCS for pyridine *N*-oxides and *N*-benzyloxypyridine perchlorates in $(CD_3)_2SO$ and chemical shifts for the parent derivatives

		C-2		C-3		C-4		C-5		C-6	
X	R	N–O	N–OBz	N–O	N–OBz	N–O	N–OBz	N–O	N–OBz	N–O	N–Obz
4-NMe_2	H	−0.75	−2.82	−18.28	−21.89	22.30	10.0	−18.28	−21.89	−0.75	−2.82
4-OMe	H	0.66	1.25	−14.30	−15.37	31.70	24.80	−14.30	−15.37	0.66	1.25
4-Me	H	−0.81	−1.23	0.38	0	10.78	13.64	0.38	0	−0.81	−1.23
4-Bu^t	H	−0.86	−0.96	−1.20	−3.16	23.84	24.52	−1.20	−3.16	−0.86	−0.96
$X = R^2 = R^6 = H$		138.75	141.74	126.51	129.23	124.83	145.35	126.51	129.23	138.75	141.74
4-NMe_2	2-Me	−0.57	−4.28	−18.03	−23.15	22.60	10.70	−16.82	−20.24	−0.29	−2.57
4-OMe	2-Me	1.01	0.80	−14.61	−16.63	31.99	24.86	−13.42	−14.07	0.88	1.13
4-Me	2-Me	−0.93	−1.54	1.44	−1.37	10.83	12.48	0.54	4.32	−0.75	−1.56
$X = R^6 = H, R^2 = Me$		147.81	153.47	126.46	130.29	124.51	144.56	123.86	126.84	138.59	141.60
4-NMe_2	2,6-Me_2	−0.92	−4.10	−17.27	−21.48	22.34	10.91	−17.27	−21.48	−0.92	−4.10
4-OMe	2,6-Me_2	0.81	0.64	−14.00	−15.42	31.66	24.67	−14.00	−15.42	0.81	0.64
4-Me	2,6-Me_2	−0.87	−1.56	0.58	4.32	10.65	13.01	0.58	4.32	−0.87	−1.56
$X = H, R^2 = R^6 = Me$		147.70	153.64	123.93	128.09	123.45	143.99	123.93	128.09	147.70	153.64
3-OMe	H	−11.91	−13.17	30.94	29.77	−13.00	−15.92	−0.81	1.61	−7.09	−7.72
3-Me	H	−0.48	1.05	10.13	9.47	1.08	0.28	2.33	−1.09	−1.09	−0.73
3-Me	5-Me	−0.06	−1.60	10.24	9.96	1.30	0.43	−0.81	−0.60	−2.55	−1.28
3-Me	4-Me	0.03	−1.22	8.60	8.84	0.08	−1.94	−0.16	−0.75	−2.35	−1.12

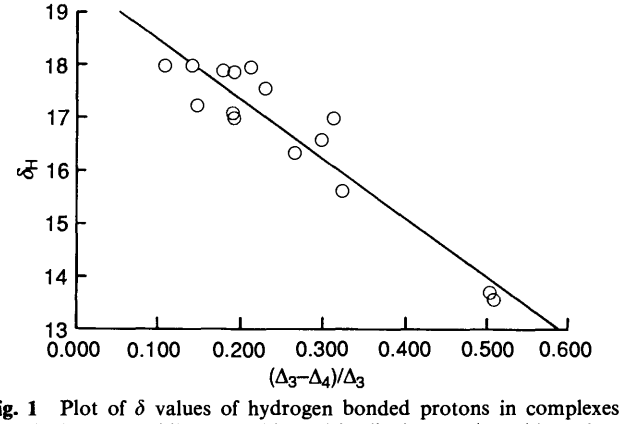


Fig. 1 Plot of δ values of hydrogen bonded protons in complexes of substituted pyridine *N*-oxides with dichloroacetic acid against $(\Delta_3 - \Delta_4)/\Delta_3$

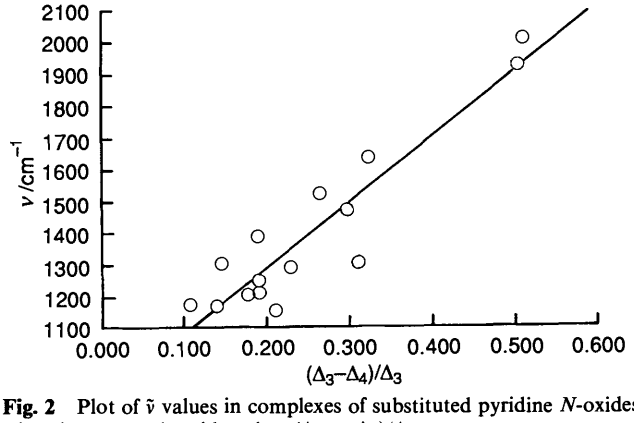


Fig. 2 Plot of $\tilde{\nu}$ values in complexes of substituted pyridine *N*-oxides with dichloroacetic acid against $(\Delta_3 - \Delta_4)/\Delta_3$

Results and Discussion

SCS* values for the compounds investigated are given in Tables 1–3. The shifts were measured for samples in $(CD_3)_2SO$, $CDCl_3$, 80% DCA, D_2O and 60% $HClO_4$. Positive SCS values indicate a downfield shift from pyridine *N*-oxide, monomethyl- or dimethyl-pyridine *N*-oxide. The chemical shift of any of the ring carbons relative to Me_4Si can easily be calculated by adding the SCS to the shift of the parent compound listed in each table. In each table the first column lists the variable substituents (X) for a given series. The row of substituents at the head of the table indicates the different series. If additivity were operative, then all SCS in a given row would be constant, *i.e.* the Y substituent * would not affect the SCS of X.

SCS data for monosubstituted benzenes show a slight solvent dependence.[17] The lack, to our knowledge, of SCS values for D_2O and $HClO_4$ prompted us to use SCS values for chloroform.

The SCS values for substituted pyridine *N*-oxides in $CDCl_3$, differ (up to *ca.* 6 ppm) from SCS values for substituted benzenes. The range of these differences is considerably smaller than that for the corresponding 1,4- and 1,3-disubstituted benzenes.[11] Protonation or *O*-alkylation of pyridine *N*-oxides strongly increases the difference (up to *ca.* 12.5 ppm). The variation of SCS demonstrates that non-additivity is clearly present in 3-X- and 4-X-pyridine *N*-oxides. In 3-X-pyridine *N*-oxides the range of variation in SCS values is similar for different ring positions. This is in contrast with 4-X-pyridine *N*-oxides, where large variations are observed at the *ipso* position, while smaller SCS variations are found at *ortho* and *meta* sites. A similar order of changes was observed for 1,3- and 1,4-disubstituted benzenes.[11]

The data given in Table 2 show that the chemical shift of C-6 in the 3-X-pyridine *N*-oxides and their protonated or *O*-methylated derivatives is influenced by the substituent X in a way similar to the *para* shifts in 1,4- and 1,3-disubstituted benzenes. The SCS values for a range of X substituents fit the dual substituent parameter, DSP, eqn. (1), with good precision

$$\delta_{SCS} = \rho_I\sigma_I + \rho_R\sigma_R^\circ \quad (1)$$

(*N*-oxides: $\rho_I = 4.08$; $\rho_R = 21.99$; SD = 0.70; $R = 0.992$; protonated and *O*-alkylated derivatives: $\rho_I = 4.03$; $\rho_R = 18.59$; SD = 0.53; $R = 0.992$). The polar (σ_I) and resonance (σ_R°) substituent constants are taken from ref. 18. These data show that both field and resonance parameters of the variable substituent contribute to changes in the chemical shifts at this site; the resonance effect is *ca.* four times larger than the field effect.

* Substituent chemical shifts (SCS) are quoted with respect to the corresponding unsubstituted pyridine *N*-oxide or its methyl or dimethyl derivatives, where *j* indicates the position (*ortho*, *meta*, *para*) of the carbon atom with respect to the variable group, X. $SCS_{jX}^{Y} = \delta(XC_5H_{4-n}R_nY) - \delta(HC_5H_{4-n}R_nY)$; Y = N–O, N^+–OH, N^+–OMe, N^+–OCH_2Ph.

Table 2 ^{13}C SCS for pyridine *N*-oxides in D_2O or 60% $HClO_4$, and perchlorates of *N*-methoxypyridines in D_2O

		C(2)		C(3)		C(4)		C(5)		C(6)	
X	R	D_2O	$HClO_4$	D_2O	$HClO_4$	D_2O	$HClO_4$	D_2O	$HClO_4$	D_2O	$HClO_4$
4-NMe_2	H	−1.08	−1.13	−19.95	−21.35	19.18	12.08	−19.95	−21.35	−1.08	−1.13
4-OMe	H	1.09	2.00	−14.58	−15.37	29.90	26.44	−14.58	−15.37	1.09	2.00
4-OEt	H	1.74	2.01	−13.55	−15.11	29.96	25.58	−13.55	−15.11	1.74	2.01
4-OPh	H	1.41	2.38	−12.55	−13.87	28.63	24.60	−12.55	−13.87	1.41	2.38
4-Cl	H	0.92	1.03	0.15	0.27	6.17	7.75	0.15	0.27	0.92	1.03
4-Br	H	0.87	0.44	3.14	3.36	−6.45	−4.01	3.14	3.36	0.87	0.44
4-Me	H	−0.92	−0.87	0.43	0.16	12.67	14.52	0.43	0.16	−0.92	−0.86
4-Me[a]	H		−1.35		0.21		14.83		0.21		−1.35
4-Bu^t	H	−0.87	−0.92	−2.99	−3.14	24.75	25.09	−2.99	−3.14	−0.87	−0.92
4-COMe	H	0.60	0.76	−1.42	−1.74	4.06	2.28	−1.42	−1.47	0.60	0.76
4-CN	H	1.19	0.98	2.97	3.19	−16.26	−18.85	2.97	3.19	1.19	0.98
4-NO_2	H	3.58	1.03	−5.75	−5.69	13.97	10.46	−5.75	−5.69	3.58	1.03
X = R^2 = R^6 = H		139.73	140.54	128.09	129.71	133.07	144.28	128.09	129.71	139.73	140.54
4-NMe_2	2-Me	−1.31	−2.36	−20.32	−22.43	19.91	12.52	−18.35	−19.66	−1.07	−1.17
4-OMe	2-Me	1.21	1.52	−15.52	−16.69	30.02	31.28	−13.71	−14.03	3.97	1.63
4-Me	2-Me	−0.81	−1.30	0.48	0.0	13.28	14.36	0.71	0.49	−0.86	3.98
4-NO_2[b]	2-Me	2.44	0.76	−5.93	−5.74	9.48	13.49	−7.53	−6.01	1.79	2.71
X = R^6 = H, R^2 = Me		150.08	153.55	128.47	130.74	132.04	143.74	125.32	126.89	139.73	141.14
4-NMe_2	2,6-Me_2	−1.18	−1.14	−18.77	−20.74	20.95	14.74	−18.77	−20.74	−1.18	−1.14
4-OMe	2,6-Me_2	1.25	2.09	−14.50	−15.14	29.91	26.81	−14.50	−15.14	1.25	2.09
4-OEt	2,6-Me_2	1.19	1.03	−14.18	−14.93	29.15	26.22	−14.18	−14.93	1.19	1.03
4-Cl	2,6-Me_2	1.19	−0.54	−0.25	−0.70	5.42	6.29	−0.25	−0.70	1.19	−0.54
4-I	2,6-Me_2	0.92	−0.31	8.90	9.48	−34.94	−28.85	8.90	9.48	0.92	−0.31
4-Me	2,6-Me_2	−1.09	−1.33	0.40	0.46	11.76	15.22	0.40	0.46	−1.09	−1.33
4-Me[a]	2,6-Me_2		−1.71		0.33		14.20		0.33		−1.71
4-NO_2	2,6-Me_2	2.39	−1.89	−6.20	−6.93	12.90	14.58	−6.20	−6.93	2.39	−1.89
X = H, R^2 = R^6 = Me		150.19	155.93	125.68	128.62	130.68	144.06	125.62	128.62	150.19	155.93
3-NMe_2	H	−16.09	−4.60	21.50	12.63	−16.69	−7.88	−1.20	1.90	−12.94	2.50
3-OMe	H	−12.89	−11.91	30.88	30.23	−14.04	−15.11	−0.49	−0.05	−8.07	−7.12
3-Cl	H	−0.43	−0.48	6.44	6.88	−0.27	−0.21	−0.16	0.05	−1.30	−1.24
3-Cl[a]	H		−0.14		6.93		0.05		0		−1.26
3-Br	H	1.52	1.36	−6.45	−6.34	2.44	2.52	0.05	0.06	−0.97	−1.02
3-Me	H	−0.34	−0.48	11.16	12.30	0.68	0.66	−0.93	−1.03	−3.07	−2.86
3-Me[a]	H		−0.71		12.41		0.58		−1.11		−3.29
3-COMe	H	−0.21	1.41	8.45	7.64	−1.58	−1.08	−5.96	0.49	3.25	3.10
3-COMe[a]	H		0.59		7.91		−1.16		0.43		2.76
3-CN	H	3.26	3.74	−14.58	−14.78	2.22	2.82	0.59	0.92	4.23	4.07
3-CN[a]	H		4.29		−14.65		3.17		0.78		3.98
3-NO_2	H	−3.14	−2.27	16.79	17.72	−4.99	−5.93	−1.47	0.92	5.15	5.05
X = R^2 = R^6 = H		139.39	140.06	139.25	142.01	133.75	144.94	127.16	128.68	133.66	137.68
3-Me	4-Me	−0.41	0.63	9.52	9.05	−0.99	−1.94	−0.50	−0.69	−2.55	−2.50
3-Me	6-Me	−0.54		11.00		1.14		−0.82		−3.19	
3-Me[a]	6-Me		−1.03		11.97		0.95		−1.08		−3.41

[a] SCS values for perchlorates of *N*-methoxypyridines in D_2O. [b] SCS values in D_2O with 10% of MeOH.

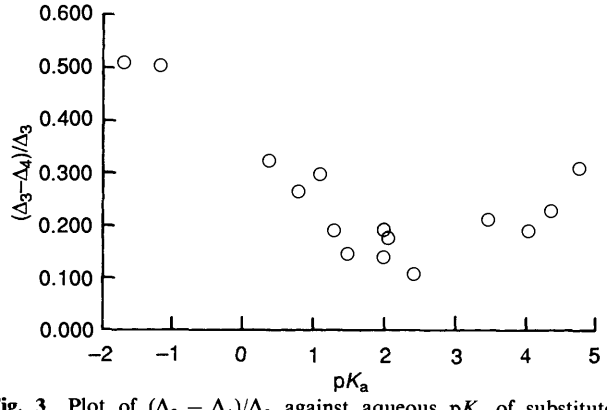


Fig. 3 Plot of $(\Delta_3 - \Delta_4)/\Delta_3$ against aqueous pK_a of substituted pyridine *N*-oxides

Large variations in the SCS values from the corresponding values in monosubstituted benzenes indicated important substituent–substituent interactions especially for *O*-alkylated or protonated species. This is illustrated in Tables 4 and 5, where the X-induced SCS are correlated with the corresponding values in benzenes. The slopes deviate from the expected unity if strict additivity were operative. The larger standard deviation (Table 4), a factor of two, estimated for *N*-oxides in 80% DCA and 60% $HClO_4$, and also for *O*-alkylated derivatives in Me_2SO indicate that interactions of N–O and N^+–OR (R = H, Me, CH_2Ph) with X are different. The observed non-additive sites in substituted pyridine *N*-oxides are similar to those found in 1,3- and 1,4-disubstituted benzenes[11] which result from a mutual interaction between substituents.

We have previously shown that solute–solvent interactions have a significant effect on the ^{13}C chemical shifts of pyridine *N*-oxide.[19] The largest variations of the chemical shift occur when the lone pair of the oxygen forms a hydrogen bond with protic solvents or is protonated. That variation decreases in the order C-4 > C-3 > C-2. Now we find that the magnitude strongly depends on the substituent involved (Table 6).

Detection of hydrogen bonding can be made significantly more difficult by medium polarity effects and by protonation. In

Table 3 ^{13}C SCS for substituted pyridine *N*-oxides in $CDCl_3$ and 80% dichloroacetic acid (DCA) in $CDCl_3$

		C(2)		C(3)		C(4)		C(5)		C(6)	
X	R	N–O	DCA	N–O	DCA	N–O	DCA	N–O	DCA	N–O	DCA
4-NMe_2	H	−0.15	−0.88	−18.35	−21.13	20.21	15.74	−18.35	−21.13	−0.15	−0.88
4-OMe	H	0.71	1.98	−14.39	−14.89	29.18	29.81	−14.39	−14.89	0.71	1.98
4-OEt	H	0.86	1.94	−13.94	−14.67	29.47	28.76	−13.94	−14.67	0.86	1.94
4-Cl	H	0.87	1.12	0.36	−0.09	5.97	6.24	0.36	−0.09	0.87	1.12
4-Me	H	−0.63	−0.89	0.63	0.51	9.35	15.38	0.63	0.51	−0.63	−0.89
4-$C_{11}H_{23}$	H	−0.60	−0.65	−0.18	−0.38	14.52	19.47	−0.18	−0.38	−0.60	−0.65
4-Bu^t		−0.77	−0.77	−3.03	−2.97	22.61	27.18	−3.03	−2.97	−0.77	−0.77
4-COMe	H	0.49	1.09	−0.89	−1.94	4.46	0.69	−0.89	−1.94	0.49	1.09
4-CN	H	1.27	1.38	2.96	2.12	−18.02	−22.81	2.96	2.12	1.27	1.38
4-NO_2	H	1.05	2.19	−5.13	−6.55	14.08	8.97	−5.13	−6.55	1.09	2.19
X = R^2 = R^6 = H		139.16	139.80	126.03	128.12	125.82	139.38	126.03	128.12	139.16	139.80
4-NMe_2	2-Me	−0.39	−2.01	−17.56	−22.33	21.91	14.56	−17.12	−19.73	−0.07	−0.53
4-OMe	2-Me	0.93	1.84	−16.04	−17.32	31.30	28.01	−13.59	−13.74	0.78	2.28
4-Me	2-Me	−0.84	−0.66	1.67	0.38	10.44	14.52	0.78	0.81	−0.60	−0.33
X = R^6 = H, R^2 = Me		148.89	152.10	125.36	129.08	126.39	140.52	123.43	125.53	139.20	139.86
4-NMe_2	2,6-Me_2	−0.71	−2.91	−17.62	−20.82	20.95	14.73	−17.62	−20.82	−0.71	−2.91
4-OMe	2,6-Me_2	0.66	1.07	−14.26	−14.98	32.23	28.05	−14.26	−14.98	0.66	1.07
4-Me	2,6-Me_2	−0.95	−1.20	0.74	0.61	11.93	15.07	0.74	0.61	−0.95	−1.20
X = H, R^2 = R^6 = Me		149.01	153.34	123.87	126.41	124.25	139.79	123.87	126.41	149.01	153.41
3-OMe	H	−11.41	−12.13	31.91	30.19	−15.42	−12.27	−0.71	−3.53	−6.75	−7.65
3-Me	H	−0.09	0.96	10.66	12.00	−0.69	−0.24	−0.90	−0.76	−2.80	−2.89
3-Me	4-Me	0.08	−0.76	10.56	10.25	−2.06	−0.68	−0.15	−0.40	−2.41	−2.37
3-Me	5-Me	−0.55	−0.55	9.13	14.73	3.53	0.17	−0.52	1.97	−3.26	−4.40

Table 4 Proportionality relationships between 4-X-pyridine *N*-oxides, their protonated and *O*-alkylated derivatives and benzenes[a]

Solvent	R	Y	SCS	a_0	b	r	SD	n
$CDCl_3$	H, Me	N–O	*ipso*	0.546	0.924	0.984	2.327	15
$(CD_3)_2SO$	H, Me	N–O	*ipso*	1.071	0.976	0.998	0.709	11
D_2O	H, Me	N–O	*ipso*	−0.707	0.980	0.991	2.544	17
DCA	H, Me	N–O·H, N^+–OH	*ipso*	−1.424	0.938	0.907	5.971	15
$(CD_3)_2SO$	H, Me	N^+–OCH_2Ph	*ipso*	3.768	0.602	0.776	5.333	11
$HClO_4$	H, Me	N^+–OH	*ipso*	−0.259	0.849	0.957	4.896	17
$CDCl_3$	H, Me	N–O	*ortho*	−0.041	1.077	0.993	0.981	18
$(CD_3)_2SO$	H, Me	N–O	*ortho*	−0.140	1.050	0.986	1.439	11
D_2O	H, Me	N–O	*ortho*	−0.456	1.104	0.989	1.431	19
DCA	H, Me	N–O·H, N^+–OH	*ortho*	−0.535	1.179	0.979	1.948	18
$(CD_3)_2SO$	H, Me	N^+–OCH_2Ph	*ortho*	1.426	1.344	0.974	2.481	11
$HClO_4$	H, Me	N^+–OH	*ortho*	−0.518	1.176	0.989	1.428	15

[a] SCS values for substituted benzenes are taken from ref. 17.

Table 6 the hydrogen bonding effect on C-4 has been tentatively estimated as the difference in the chemical shift between aqueous and chloroform solutions [$\Delta_1 = \delta(D_2O) - \delta(CDCl_3)$], and the protonation effect as a difference in the chemical shift between perchloric acid and aqueous solutions [$\Delta_2 = \delta(HClO_4) - \delta(D_2O)$]. Data listed in Table 6 show that substituents alter appreciably both hydrogen-bonding and protonation effects. Some substituents increase (4-Me, 4-Bu^t, 4-Cl), while others decrease (4-NMe_2, 4-OMe, 4-NO_2, 4-COMe) Δ_1 and Δ_2 in comparison with reference data (X = H). Substituents like 4-CN increase one effect but decrease another. Substituents at C-3 change Δ_1 and Δ_2 in a way different from substituents at C-4.

Complexes of substituted pyridine *N*-oxides with dichloroacetic acid in CH_2Cl_2 were investigated by IR and ^1H NMR spectroscopy.[20] A gradual proton transfer from the acid to pyridine *N*-oxides *via* strengthening intermolecular H-bonds, AH ··· ON, and further by weakening of interionic H-bonds, A^- ··· HON^+ has been considered. Since DCA is a stronger proton donor than water, $\Delta_4 = \delta(DCA) - \delta(CDCl_3)$, as expected, is larger than Δ_1 and increases with increasing pK_a. For the most basic *N*-oxides Δ_4 closely approached Δ_3 [$\Delta_3 = \delta(HClO_4) - \delta(CDCl_3)$]. Figs. 1 and 2 show correlations of the chemical shifts of the H-bonded protons and the centre of gravity, $\tilde{\nu}$, due to protonic vibration with the relative ^{13}C chemical shift difference $[(\Delta_3 - \Delta_4)/\Delta_3]$ listed in Table 6. The least-squares equations for the data are given below.

$$\delta_H = 19.576 - 11.182\frac{\Delta_3 - \Delta_4}{\Delta_3};$$

$$r = 0.940, \text{SD} = 0.510, n = 15$$

$$\tilde{\nu} = 877.14 + 2072.2\frac{\Delta_3 - \Delta_4}{\Delta_3};$$

$$r = 0.926, \text{SD} = 105.5, n = 15$$

Standard deviations are slightly larger than the experimental error.[20] This is partly due to the excess of acid, as the ^1H NMR and IR spectra were measured as the 1:1 acid–base mixtures. When the acid is present in the excess in the mix-

Table 5 Proportionality relationships between 3-X-pyridine *N*-oxides, their protonated and *O*-alkylated derivatives and benzenes[a]

Solvent	R	Y	SCS	a_0	b	r	SD	n
D_2O	H, Me	N–O	*ipso*	0.345	0.955	0.995	1.351	11
D_2O	H, Me	N^+–OH, N^+–OMe	*ipso*	0.631	0.964	0.991	1.678	14
D_2O	H, Me	N–O	*para*	−0.213	1.005	0.991	0.739	11
D_2O	H, Me	N^+–OH, N^+–OMe	*para*	−0.158	0.862	0.990	0.520	14
D_2O	H, Me	N–O	*ortho* (2)	−0.550	0.912	0.988	0.975	11
D_2O	H, Me	N^+–OH, N^+–OMe	*ortho* (2)	−0.057	0.745	0.959	1.112	14
D_2O	H, Me	N–O	*ortho* (4)	−0.652	0.979	0.992	0.838	11
D_2O	H, Me	N^+–OH, N^+–OMe	*ortho* (4)	−0.668	1.010	0.988	0.752	14

[a] SCS values for substituted benzenes are taken from ref. 17.

Table 6 Difference and relative ^{13}C chemical shifts for C-4 in substituted pyridine *N*-oxides

Pyr. *N*-oxide	pK_a[a]	Δ_1[b]	Δ_2[c]	Δ_3[d]	Δ_4[e]	$(\Delta_3 - \Delta_4)/\Delta_3$	δ_H[a]	ν[a]
4-NO_2	−1.70	4.83	7.70	12.53	6.15	0.509	13.56	2011
4-CN	−1.17	9.19	5.78	17.81	8.84	0.504	13.70	1927
4-Cl	0.36	7.64	12.79	20.43	13.83	0.323	15.62	1639
H	0.79	7.25	11.21	18.46	13.56	0.265	16.33	1522
3-Me	1.08	8.62	11.19	19.81	13.90	0.298	16.58	1471
4-Me	1.29	8.26	13.06	21.32	17.29	0.189	17.09	1390
3,4-Me_2	1.48	7.64	12.11	19.75	16.86	0.146	17.22	1303
2,4,6-Me_3	1.99	6.26	16.84	23.10	18.68	0.191	16.98	1209
4-OEt	1.97	5.44	6.83	12.27	10.55	0.140	17.97	1169
4-OMe	2.05	5.16	7.75	12.91	10.63	0.177	17.88	1205
4-OMe-2-Me	2.41	4.35	7.63	12.16	10.84	0.108	17.96	1175
4-OMe-2,6-Me_2	3.45	4.11	10.28	14.39	11.36	0.211	17.95	1151
4-NMe_2	4.05	4.28	4.11	8.39	6.79	0.191	17.85	1250
4-NMe_2-2-Me	4.35	2.99	5.05	8.82	6.80	0.229	17.55	1291
4-NMe_2-2,6-Me_2	4.75	5.63	7.97	13.60	9.36	0.312	16.98	1304

[a] Values from ref. 12; [b] $\Delta_1 = \delta(D_2O) - \delta(CDCl_3)$. [c] $\Delta_2 = \delta(HClO_4) - \delta(D_2O)$. [d] $\Delta_3 = \delta(HClO_4) - \delta(CDCl_3)$. [e] $\Delta_4 = \delta(DCA) - \delta(CDCl_3)$.

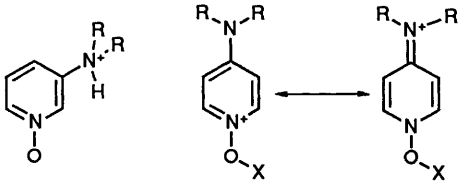
Table 7 ^{13}C chemical shifts of the NMe group in *N*,*N*-dimethylaminopyridine *N*-oxides in D_2O and 60% $HClO_4$

N-Oxide	D_2O	$HClO_4$
4-NMe_2	39.66	40.53
4-NMe_2-2-Me	39.59	39.68
4-NMe_2-2, 6-Me_2	39.45	39.80
3-NMe_2	39.88	48.71

ture, considerably more proton transfer to the base occurs than with the 1:1 mixture.[21] A second reason may be a solvent effect; SCS is slightly solvent dependent and $(\Delta_3 - \Delta_4)/\Delta_3$ was derived from SCS in three solvents.

As the chemical shift and the centre of gravity are a measure of the hydrogen-bond strength and protonation, thus the correlations shown in Figs. 1 and 2, demonstrate that the $(\Delta_3 - \Delta_4)/\Delta_3$ values are also a measure of these two effects and are not influenced by the substituent effects. The correlation of $(\Delta_3 - \Delta_4)/\Delta_3$ with aqueous pK_a values for pyridine *N*-oxides shown in Fig. 3 supports this conclusion. Previously, we have reported the same type of correlation between either the chemical shift of hydrogen-bonded protons, or the centre of the complex infrared absorption and pK_a.[20]

Finally, the position of protonation of 3- and 4-dimethylaminopyridine *N*-oxides requires some comments. In aminopyridines and their *N*,*N*-dimethylamino derivatives the first protonation is much easier relative to the second and the monocation seems to be derived from protonation at the heterocyclic nitrogen.[22] Aminopyridine *N*-oxides are protonated at oxygen as predicted theoretically[23] and confirmed by ultraviolet spectral comparisons.[24] The SCS values are extremely sensitive to protonation of exocyclic NH_2, NHMe and NMe_2 groups bonded to aromatic systems.[17] The observed large differences in the SCS values for *ipso*, *ortho* and *para* positions between free and protonated species (Table 2) indicate that 3-dimethylaminopyridine *N*-oxide is protonated at the dimethylamino group. Similar *ortho* SCS values of free, protonated and *O*-alkylated compounds on the one hand and differences in *ipso* SCS values between free and protonated or *O*-alkylated derivatives on the other, indicate that 4-dimethylaminopyridine *N*-oxide is protonated on the oxygen atom. The stabilization of ions of type **4b** is more effective than is the corresponding stabilization in the free base, and this is responsible for the observed difference in the *ipso* SCS.



3 **4a** **4b**

X = H, CH_2Ph

The chemical shifts of the NMe group (Table 7) confirm the conclusion that only 3-dimethylaminopyridine *N*-oxide is protonated at the dimethylamino group.

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