The Influence of Steric Effect on ^{1}H NMR, ^{13}C NMR, and IR Spectra of Methylated Derivatives of 4-Nitropyridine *N*-Oxide

A. PUSZKO and L. WASYLINA

Department of Organic Chemistry, Academy of Economics, PL-53 345 Wrocław

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The ^{1}H NMR, ^{13}C NMR, and IR spectra of 2-methyl-, 3-methyl-, 2,3-dimethyl-, 2,5-dimethyl-, 2,6-dimethyl-, 3,5-dimethyl-, and 2,3,6-trimethyl-4-nitropyridine *N*-oxides were interpreted. The influence of electron properties of substituents on changes of chemical shifts was analyzed. It was found that "*ortho*-effect" of the methyl group inhibits paramagnetism of the nitro group. The ratio between a given substituted heterocyclic compound, its parent compound and the identically substituted benzene derivatives has been determined. It was found that the effect of the nitro group on chemical shift and the so-called back donation is modified by electronegativity and the position of the substituent.

The chemistry of heterocyclic *N*-oxides has gained importance due to the interesting biological activities of these compounds [1]. The antifungal activities of 4-nitropyridine *N*-oxide and its 2-methyl derivative are well known [2, 3].

The ^{1}H NMR spectra of pyridine *N*-oxides depend significantly on the acidity of the solvent, *i.e.* its tendency to coordinate with a lone pair of electrons on oxygen in the *N*-oxide group. The spectra in carbon tetrachloride solution are the closest to being those of the free bases, while in 9 M sulfuric acid the species under study are the *N*-hydroxypyridinium salts.

Pyridine *N*-oxide shows a shielding effect of protons (δ = 0.3) at C-2, C-4 and a deshielding one (δ = 0.15) at C-3 relative to the corresponding pyridine [1]. In the literature there are not many data dealing with the coupling constant of disubstituted pyridine *N*-oxides [4]. It was interesting to learn how the presence of two or three substituents (one methyl or two methyl groups and one nitro group), which are situated in various positions of pyridine ring affects not only the chemical shifts of protons and carbons but also the coupling constant of protons.

Substituent effect on reactivities and physical properties of substituted pyridine *N*-oxides or the related compounds have been investigated by means of N—O stretching frequencies [5, 6] and ^{13}C NMR [6] and ^{17}O NMR [7] spectroscopy.

In our physicochemical research on the reactivity of the interesting class of compound, *i.e.* *N*-oxides of 2-halopicoline, their 4-halo and 4-nitro derivatives, *N*-oxides of 2-halopyridinecarboxylic acid, picoline-2-thiol and picoline-2,4-dithiol [8, 9], of 3-halo-2,6-dimethylpyridine and its 4-nitro derivative, it was purposeful to measure the ^{13}C NMR spectra of methylated derivatives of 4-nitropyridine *N*-oxide since they can provide many interesting data about the structure of these molecules and the interaction of the methyl group with the pyridine ring.

The present paper is concerned with the effect of the substituents and of their interaction on the changes of the back donation of *N*-oxide group.

IR spectra of pyridine *N*-oxides are characterized by two strong absorption bands in the region of $\tilde{\nu}$ = 1200—1300 cm^{-1} and 835 cm^{-1} The position of a band in the 1200—1300 cm^{-1} region is very sensitive to the presence of substituent [10]. Hydrogen bonding results in a shift of this band to lower wavenumbers. The wavenumber of ν(NO) is higher in pyridine *N*-oxides compared to the aliphatic ones, which has been attributed to the back donation of the *N*-oxide group [1].

The nature of the substituents and their position in pyridine *N*-oxide influences the ν(NO). The electron-withdrawing group, contrary to the electron-donating one, shifts this band to higher wavenumbers.

EXPERIMENTAL

The methyl derivatives of 4-nitropyridine *N*-oxide used in the study were synthesized by previously described methods [11—15].

The ^{1}H NMR spectra of title compounds were taken on a Tesla BS 589 A apparatus (100 MHz) at the temperature of 30 °C. $CDCl_3$ has been used as a solvent and TMS as an internal standard. The chemical shifts of protons and coupling constants of methyl derivatives of 4-nitropyridine *N*-oxide are collected in Table 1.

The ^{13}C NMR spectra were recorded on a Tesla BS 589 A spectrometer at 25.142 MHz. Typical conditions: spectral width 7600 Hz, 8K data points, pulse

Table 1. Chemical Shifts δ (Experimental and (Calculated)) and Coupling Constants of Methyl Derivatives of 4-Nitropyridine *N*-Oxide

Derivative	δ					Coupling constants
	H-2	H-3	H-5	H-6	CH_3	
2-Methyl		8.00	8.00	8.20	2.48 (2)	$J_{5,6}$ = 6.0 Hz
		(8.00)	(7.99)	(8.28)		
3-Methyl	8.00		8.00	8.00	2.50 (3)	
	(8.20)		(8.08)	(8.19)		
2,3-Dimethyl			7.60	8.10	2.48 (2,3)	$J_{5,6}$ = 7.0 Hz
			(7.90)	(8.10)		
2,5-Dimethyl		7.93		8.13	2.48 (2)	
		(7.93)		(8.11)	2.42 (5)	
2,6-Dimethyl		7.95	7.95		2.48 (2,6)	
		(7.82)	(7.82)			
3,5-Dimethyl	7.93			7.93	2.23 (3,5)	
	(8.02)			(8.02)		
2,3,6-Trimethyl			7.56		2.80 (2,6)	
			(7.73)		2.73 (5)	

Table 2. ^{13}C NMR Chemical Shifts δ (Experimental and (Calculated)) and ρ^{13} of Methyl Derivatives of 4-Nitropyridine *N*-Oxide in $CDCl_3$

Derivative	δ							ρ^{13}
	C-2	C-3	C-4	C-5	C-6	C—CH_3		
2-Methyl	151.12	121.17	142.24	118.63	140.59	C-2—CH_3	18.46	0.824
	(151.03)	(123.38)	(142.10)	(120.27)	(141.42)			
3-Methyl	142.16	133.42	143.58	122.52	138.43	C-3—CH_3	18.62	0.885
	(141.13)	(133.69)	(144.02)	(122.35)	(138.47)			
2,3-Dimethyl	151.20	130.14	144.70	118.56	137.76	C-2—CH_3	14.66	0.850
	(150.86)	(134.47)	(143.22)	(120.19)	(138.59)	C-3—CH_3	16.22	
2,5-Dimethyl	148.58	122.29	143.13	130.36	142.08	C-2—CH_3	17.79	0.850
	(148.21)	(123.10)	(143.22)	(131.56)	(141.25)	C-5—CH_3	18.16	
2,6-Dimethyl	150.97	118.48	141.26	118.48	150.97	C-2—CH_3	18.98	0.788
	(151.16)	(121.25)	(141.30)	(121.25)	(151.16)	C-6—CH_3		
3,5-Dimethyl	139.32	129.92	147.10	129.92	139.32	C-3—CH_3	15.93	0.908
	(138.30)	(133.41)	(145.14)	(133.41)	(138.30)	C-5—CH_3		
2,3,6-Trimethyl	151.49	127.22	144.62	118.70	148.06	C-2—CH_3	15.55	0.816
	(150.98)	(132.34)	(142.42)	(120.97)	(148.32)	C-3—CH_3	16.37	
						C-6—CH_3	18.76	

angle 90° (13 s), and repetition time 2 s. These conditions appeared digitally. All the spectra were measured in *ca.* 10 % $CDCl_3$ as a solvent and the centres of the $CDCl_3$ peaks (δ = 77.21) were used as internal references.

The assignments were carried out on the basis of previous literature values [16—18], additivity rules, model studies, single resonance spectra, and ^1H NMR spectra. The ^{13}C NMR chemical shifts were calculated on the basis of additivity rules and the effects of substituents for the studied compounds (the chemical shifts for pyridine *N*-oxide ring carbons were taken from literature [1] as well as the substituents effects, *i.e.* CH_3 [16] and NO_2 [7]). The assignments for the studied compounds were carried out using coupling constant of protons of these compounds. The calculated chemical shifts compared with experimental data are listed in Table 2.

The IR spectra were recorded on a Specord IR 75 (Zeiss, Jena) spectrophotometer in KBr.

RESULTS AND DISCUSSION

In general the effect of *N*-oxide functionality, *i.e.* back donation, appears to bring about in ^1H NMR spectra (δ = 0.3) an increase of magnetic shielding of protons in α and γ positions of the ring in comparison with those in pyridine itself [4]. Conversion of 2-picoline *N*-oxide [4] to its 4-nitropyridine derivative causes the greatest change in deshielding of the proton adjacent to the nitro group (δ = 0.68) and the proton being in the resonance position with this group (δ = 0.98), *i.e.* in the position 6 (Table 1). The observed deshielding effect of H-3 or H-5 in 2-methyl-4-nitropyridine *N*-oxide and hence the lower electron density at the C-4 are consistent with

the known nucleophilic reactivity of 4-nitro derivatives of pyridine *N*-oxide [1]. Only singlets were observed in the spectra of 2,5-dimethyl-4-nitropyridine *N*-oxide, due to the lack of coupling between protons H-3 and H-6. Introduction of two substituents (nitro and methyl group) into pyridine *N*-oxide causes the change of coupling constant $J_{5,6}$ of protons in the molecule of 2-methyl-4-nitropyridine *N*-oxide from 6.5 Hz [1] to 6 Hz. Three substituents (one nitro and two methyl groups) in the molecule of 2,3-dimethyl-4-nitropyridine *N*-oxide cause the smaller change of chemical shift of H-5 ($\delta = 0.44$) than it can be expected due to steric inhibition of the mesomeric effect of the 4-nitro group. The spectra of title compounds containing one methyl group (2-methyl- and 3-methyl-4-nitropyridine *N*-oxides) and two methyl groups (2,3-dimethyl-, 2,5-dimethyl-, 2,6-dimethyl-4-nitropyridine *N*-oxides) were studied as being the ABX type and AX type, respectively.

The transition from pyridine *N*-oxide to 4-nitropyridine *N*-oxide is reflected in the largest change in the *ipso* carbon resonance frequency according to a substantial paramagnetic effect, specific to the nitro group [17]. The *ipso* deshielding effect of the nitro group in methylated derivatives of 4-nitropyridine *N*-oxide varies between $\delta = 15.56$—21.40 (Table 2). The smallest paramagnetic effect of the nitro group occurs in the spectra of 2,6-dimethyl-4-nitropyridine *N*-oxide but the highest one appears in 3,5-dimethyl-4-nitropyridine *N*-oxide. The quantity value of paramagnetic effect of the nitro group in title compounds testifies the withdrawing effect of electrons from the 2-methyl and 6-methyl group by the *N*-oxide group and from the 3-methyl and 5-methyl group by the nitro group. The comparison of calculated chemical shifts with the experimental ^{13}C NMR spectral parameters of studied compounds shows a remarkable agreement. Greater differences were found for the C-3 atom in 2,3-dimethyl-, 3,5-dimethyl-, and 2,3,6-trimethyl-4-nitropyridine *N*-oxides. The correlation of experimental chemical shifts and the calculated ones shows a large steric effect for C-4 in the molecule of 3,5-dimethyl-4-nitropyridine *N*-oxide (correlation coefficient $r = 0.720$ for carbons in the position 4, see Fig. 1 and Table 3).

The similar slopes in the correlations for C-2 and C-6 suggest that the effect of nitro substituent on corresponding chemical shifts is comparable. The disagreement between the calculated and experimental chemical shifts seems to reflect the strong electronegativity of the 4-nitro group, the substituent steric effect or the particular configurations of the substituents. The difference between the experimental chemical shifts and the calculated ones is a measure of interaction of substituents because these calculations do not take into consideration mutual interaction of a nitro group in the position 4 with the methyl groups in various positions and the *N*-oxide group. The presence of

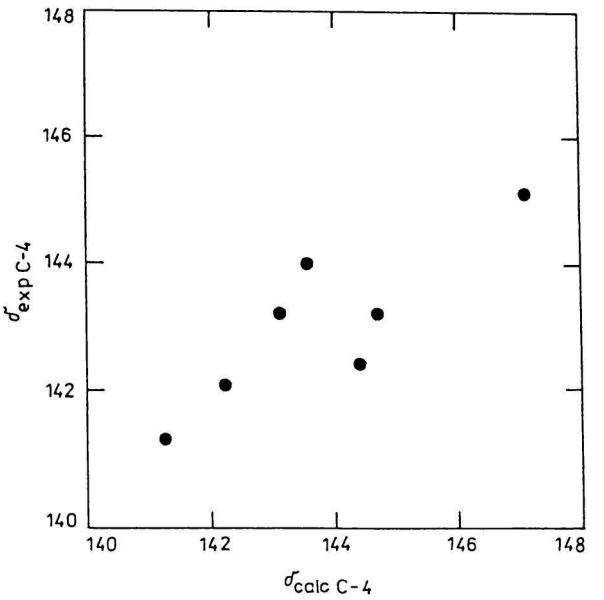


Fig. 1. A plot of δ_{expC-4} against $\delta_{calcC-4}$ for methylated derivatives of 4-nitropyridine *N*-oxide.

Table 3. Correlation Coefficient for Carbons in Different Positions

Corrrelation	r	s
$\delta_{expC-2} = 1.07\delta_{calcC-2} - 11.78$	0.998	0.259
$\delta_{expC-3} = 1.02\delta_{calcC-3} + 0.22$	0.910	1.938
$\delta_{expC-4} = 0.57\delta_{calcC-4} + 60.92$	0.720	0.738
$\delta_{expC-5} = 1.02\delta_{calcC-5} - 0.51$	0.953	1.284
$\delta_{expC-6} = 1.01\delta_{calcC-6} - 0.85$	0.980	0.799

Number of points 7, r — correlation coefficient, s — standard deviation.

four substituents (three methyl groups and one nitro group) in the molecule causes worse conformability of experimental chemical shifts to the calculated ones in comparison to monosubstituted pyridine *N*-oxides.

The π-excessive and π-deficient heterocyclic compounds can be described in the following terms

$$\rho^{13} = \frac{[\delta(\text{X-heteroarene}) - \delta(\text{H-heteroarene})]}{[\delta(\text{X-benzene}) - \delta(\text{H-benzene})]}$$

In our case

$$\rho^{13} = (\delta_{C-4}(\text{substituted pyridine } N\text{-oxide}) - \delta_{C-4}(\text{pyridine } N\text{-oxide}))/ /(\delta(\text{substituted benzene}) - \delta(\text{benzene}))$$

The substituents effects for benzene derivatives were taken from literature [19]. Based on the description, ρ^{13} should be less than 1 in the π-deficient system and greater than 1 in the π-excessive one [20]. The correlation δ(X-heteroarene) – δ(H-heteroarene) *vs.* δ(X-benzene) – δ(H-benzene) is a straight line (Fig. 2).

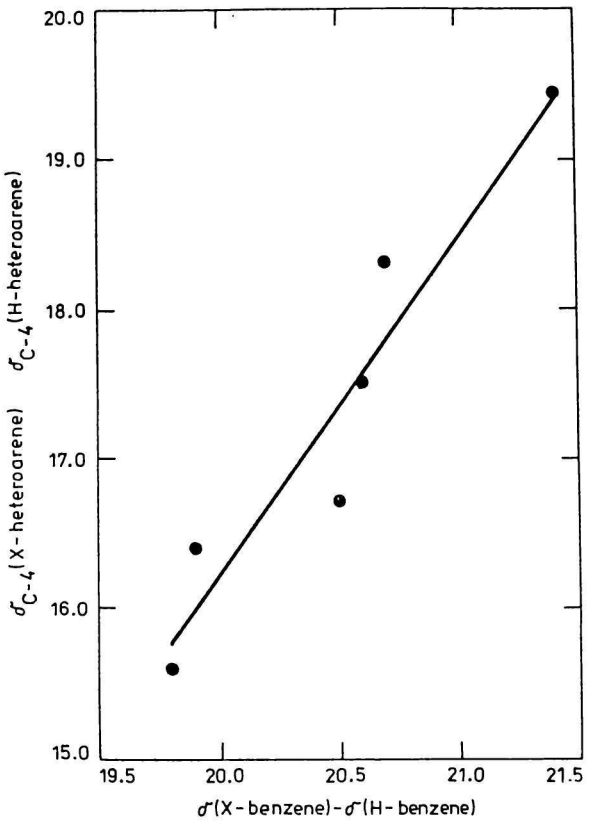


Fig. 2. ^{13}C Correlation for methylated derivatives of 4-nitropyridine *N*-oxide.

The slope of this line corresponds to ρ^{13} The general equation for this correlation is

$$\delta(\text{X-heteroarene}) - \delta(\text{H-heteroarene}) = \\ = \rho^{13} \times (\delta(\text{X-benzene}) - \delta(\text{H-benzene})) + \\ + \Delta^{13}$$

where Δ^{13} is the symbol used to represent the intercept of the plots. We have found that the straight line dependence has the following parameters: $r = 0.954$, $n = 7$, $\rho^{13} = 2.27$, $\Delta^{13} = -29.17$.

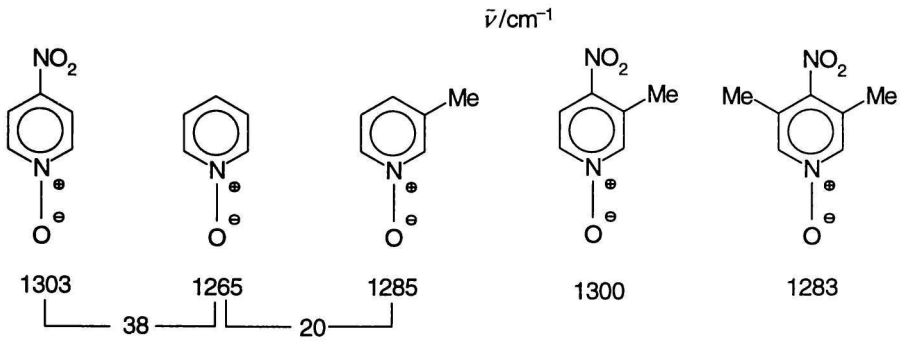
As it can be seen from Table 2, these values of ρ^{13} should help to predict the susceptibility to nucleophilic substitution of studied 4-nitropyridine *N*-oxides: ε_r(2,6-dimethyl-) > ε_r(2,3,6-trimethyl-) > ε_r (2-methyl-) > ε_r(2,3-dimethyl-) ≅ ε_r(2,5-dimethyl-) > ε_r(3-methyl-) > ε_r (3,5-dimethyl-).

The deficient system favours nucleophilic substitution. The methyl groups inhibit this substitution due to steric and positive inductive effect. The steric hindrance occurring in 2,3-dimethyl- and 3,5-dimethyl-4-nitropyridine *N*-oxide disturbs the conjugation of the nitro group with the ring.

The electron-acceptor substituent (NO_2 group) in the position 4 favours the back donation effect of the NO group. This effect is bigger than the one exerted by halogen [21] and carboxyl group [22]. However, the influence of the 4-nitro group is partially reduced due to the presence of the methyl group because the bands ν(NO) appear in lower wavenumbers (1186—1280 cm^{-1}, Table 4) in comparison with 4-nitropyridine *N*-oxide ($\tilde{\nu}$ = 1303 cm^{-1}, measured in CS_2) [1]. The wavenumbers of ν(NO) in methyl derivatives of 4-nitropyridine *N*-oxide are smaller than those in the parent compound. In 2- and 4-picoline *N*-oxide $\tilde{\nu}(\nu(\text{NO}))$ is by 5 cm^{-1} lower than in pyridine *N*-oxide, which is attributed to the electron ability of the methyl group [1]. The $\tilde{\nu}(\nu(\text{NO}))$ is lowered by the methyl group but it is increased by the 4-nitro group. The steric interaction between the methyl group and nitro group was studied by different methods. The discussion of the polarographic reduction [23] as well as of ^{15}N [18] and ^{17}O NMR data [24] confirms the occurrence of this effect. A downfield shift of the nitro group signal in 3-methyl-4-nitropyridine *N*-oxide, as compared to 4-nitropyridine *N*-oxide was discussed in terms of steric inhibition of resonance [23]. The magnitude of steric effect was evaluated on the basis of $\tilde{\nu}(\nu(\text{N}\rightarrow\text{O}))$ differences in IR spectra of *N*-oxides [21]. Characteristic bands in IR spectra of studied compounds are collected in Table 4. When summing up as in literature [23], the introducing of CH_3 group in the position 3 to the 4-nitropyridine *N*-oxide $\tilde{\nu}(\nu(\text{NO})$ = 1303 cm^{-1}) changes by 20 cm^{-1}(Scheme 1). We can calculate $\tilde{\nu}(\nu(\text{NO}))$ for 3-methyl- and 3,5-dimethyl-4-nitropyridine *N*-oxide as follows: 1265 cm^{-1} + 38 cm^{-1} + 20 cm^{-1} = 1323 cm^{-1}, 1265 cm^{-1} + 38 cm^{-1}

Table 4. IR Spectra of Methyl Derivatives of 4-Nitropyridine *N*-Oxide in KBr

Derivative	$\tilde{\nu}/cm^{-1}$				
	$\delta(NO_2)$	$\nu(N\rightarrow O)$	$\nu_s(NO_2)$	$\delta(CH_3)$	$\nu_{as}(NO_2)$
2-Methyl		1280	1338	1451	1513
3-Methyl	827	1300	1328	1458	1510
2,3-Dimethyl	837	1280	1346	1447	1519
2,5-Dimethyl	835	1254	1323	1453	1510
2,6-Dimethyl	797	1277	1339	1460	1520
3,5-Dimethyl	874	1283	1355	1448	1518
2,3-6-Trimethyl		1271	1325	1448	1517



Scheme 1

+ 20 cm^{-1} + 20 cm^{-1} = 1343 cm^{-1} The differences between these values and the experimental ones, *i.e.* 1323 cm^{-1} – 1300 cm^{-1} = 23 cm^{-1} and 1343 cm^{-1} – 1283 cm^{-1} = 60 cm^{-1}, show the efficiency of steric inhibition of resonance.

The presence of two methyl groups in the positions 3 and 5 makes steric hindrance for the nitro group and disturbs its resonance effect with the ring and thereby shifts the $\tilde{\nu}(\nu(NO_2))$ and $\tilde{\nu}(\nu(NO))$ towards lower values. The methyl groups in the positions 2 and 6 are steric hindrance for the *N*-oxide group and disturb its coupling with the ring, which is manifested by lowering $\tilde{\nu}(\nu(NO))$. This mutual interaction should decrease both $\tilde{\nu}(\nu(NO))$ and $\tilde{\nu}(\nu(NO_2))$. The effect of lowering $\tilde{\nu}(\nu(NO))$ in the molecule of 2,6-dimethyl-4-nitropyridine *N*-oxide is attributed to electron-donor ability of the methyl group ($^{+}$J, $^{+}$M).

As it was found from UV spectra [25], the twist angle of the nitro group in 3-methyl-4-nitropyridine *N*-oxide amounts to *ca.* 20° and in 3,5-dimethyl-4-nitropyridine *N*-oxide equals 60° In this case spectra can be complicated by the hydrogen bonding between *N*-oxide and the methyl group in the position 2.

The dependence of $\tilde{\nu}(\nu(NO))$ *vs.* chemical shifts of C-4 is shown in Fig. 3. The lack of correlation between chemical shifts of carbons in the position 4 and wavenumbers of the *N*-oxide group testifies the steric interaction between the substituent in the position 3 or in the positions 3 and 5 and the 4-nitro group and the disturbance of coplanarity of the nitro group with pyridine ring.

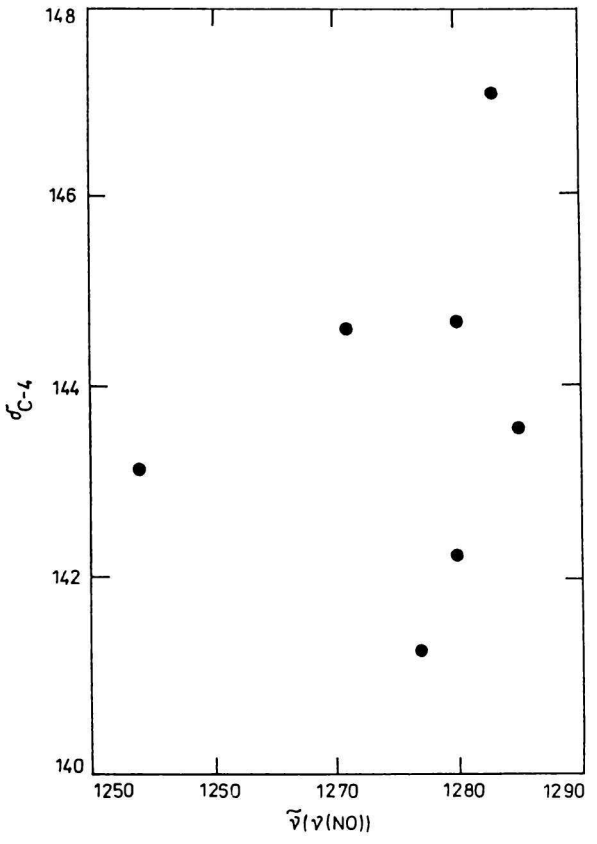


Fig. 3. A plot of δ_{C-4} against $\tilde{\nu}(\nu(NO))$ for methylated derivatives of 4-nitropyridine *N*-oxide.

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