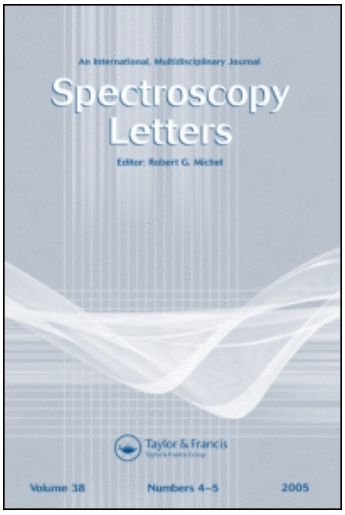

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Studies of Tertiary Amine Oxides. Part[1] 15. Carbon - 13 nuclear magnetic resonance spectra of some N-(4-substituted phenyl) piperidine, the corresponding N-oxides, and their thermal-rearrangement product

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Studies of Tertiary Amine Oxides. Part[1] 15. Carbon - 13 nuclear magnetic resonance spectra of some N-(4-substituted phenyl) piperidine, the corresponding N-oxides, and their thermal-rearrangement product.

Abdul-Hussain Khuthier*, Jasim M.A. Al-Rawi & Salim Y. Hanna, Department of Chemistry, College of Science, University of Mosul, Mosul, IRAQ.

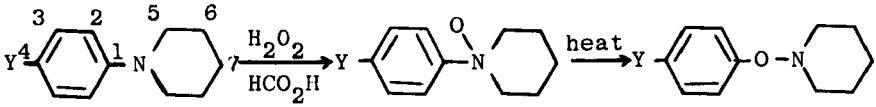
Abstract:

The carbon-13 chemical shifts of seven N-(4-substituted phenyl) piperidine; the corresponding N-oxides, and their thermal rearrangement products were analyzed and assigned. The N-oxidation effect on the carbon-13 chemical shift is discussed, a correlation of N-oxidation effect with substituent constant (σ_p, σ_m, σ_I and σ°_R) has been studied; dual substituent-parameter equation produce better correlation.

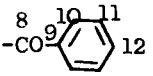
Introduction:

As part of our interest in the chemistry of tertiary amine N-oxide we have found in a recent publication[2] that

N-(4-substituted phenyl) piperidine N-oxides undergo a facile thermal isomerization to O-(4-substituted phenyl) -N-hydroxy piperidines (scheme 1) through a mechanism have named as S_NAr_i[3].



1 2 3

Compound no.	Y	Compound no.	Y
a	$-NO_2$	e	$-CO_2CH_2CH_3$ (8 9 10)
b	$-CN$ (8)	f	$-CONH_2$ (8)
c	$-COMe$ (8 9)	g	$-H$
d	$-CO$ (8)  (9 10 11 12)		

(Scheme 1)

NMR Spectroscopy is a powerful tool for studying the electronic behaviour of the N-oxide function; the N-oxidation effect on the carbon-13 chemical shift of a number of N-oxide molecules have been studied and correlated qualitatively with molecular environment[4,5]. However there have been no previous attempts in the literature to correlate quantitatively the electronic substituent constant with the N-oxidation effect on the carbon-13 chemical shift in aliphatic tertiary amine oxides. The present work is concerned with the carbon-13 chemical shift assignment and the corre-

lation of substituent chemical shift (SCS) in the N-oxidation effect (SCS $\propto \Delta\delta$ C)[11], in some N-(4-substituted phenyl) piperidine (1) (Scheme 1), with Hammett parameters[6] σ_p, σ_m, σ_p^-, and separate polar and mesomeric parameters[9] σ_I, σ_R°. Analysis of the N-oxidation effect using the dual substituent parameters(eq. 1) yield correlations with good precisions.

$$SCS = C + \rho_I \sigma_I + \rho_R \sigma_R^\circ \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (1)$$

Results and Discussion:

The assignment of carbon-13 chemical shift:

Proton decoupled as well as coupled spectra were used in the assignment of the carbon-13 chemical shift of the amines (1) (Table 1), the amine oxides (2) (Table 2) and their rearrangement products (3) (Table 3).

The para-substituent increments[7] were used to calculate the carbon-13 chemical shift of the aromatic ring carbons in the amines, and the amine oxides starting from phenyl piperidine and phenyl piperidine N-oxide respectively.

Table (1) showed the observed and the calculated carbon-13 chemical shifts of the aromatic ring carbons for the amines with a very good agreement. A gated experiment for compound 1a in which C-2, δ 112.4 (^1J = 158.4 Hz: ^2J = 5.6 Hz); C-3, δ 126 (^1J = 173.6 Hz, ^2J = 4.8 Hz) provides further support for the above assignment. Similarly the assignment of aromatic ring carbons in the N-oxide (2) was made using the first and second order couplings, for C-1 in compound 2a, δ 161.2, (^1J = 3 Hz; ^3J = 5 Hz (meta coupling[8]); C-2,

Table 1: Carbon-13 chemical shift assignment relative to TMS for N-(4-substituted phenyl) piperidine (1)

Compd. No.	C-1 (cal.)*	C-2 (cal.)*	C-3 (cal.)*	C-4 (cal.)*	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12
1 a**	155.1 (151.8)	112.4 (115.6)	126.0 (124.0)	137.8 (138.2)	48.4	25.4	24.2	-	-	-	-	-
1 b	153.7 (149.9)	113.9 (115.3)	133.3 (132.4)	98.7 (102.8)	48.2	25.2	24.2	120.2	-	-	-	-
1 c	154.0 (150.2)	113.0 (114.7)	130.2 (128.9)	126.8 (127.3)	47.4	25.9	24.0	195.2	25.9	-	-	-
1 d	153.8 (149.6)	112.9 (114.5)	131.1 (130.5)	125.0 (127.6)	47.8	24.4	23.4	193.0	139.0	128.2	132.1	128.9
1 e	154.6 (149.5)	113.6 (114.2)	131.2 (128.3)	119.2 (119.5)	48.9	25.3	24.4	166.8	60.2	14.4	-	-
1 f	153.1 (148.4)	113.5 (114.4)	128.9 (127.7)	122.8 (124.0)	48.4	24.4	23.9	167.8	-	-	-	-
1 g	146.0	114.7	128.8	118.2	50.4	25.8	24.2	-	-	-	-	-

* (Cal.) Carbon-13 chemical shift calculated using the substituent effect on the carbon-13 chemical shift of the phenyl piperidine (1g).

** Taken from reference (4).

Table 2: Carbon-13 chemical shift assignment relative to TMS for N-(-4 substituted phenyl) piperidine N-oxides (2).

Compd. No.	C-1 (cal.)*	C-2 (cal.)*	C-3 (cal.)*	C-4 (cal.)*	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12
2 a**	161.2 (161.2)	122.5 (121.0)	124.5 (123.6)	147.9 (148.7)	69.2	21.3	21.9	-	-	-	-	-
2 b	159.7 (159.3)	122.4 (120.7)	133.0 (132.0)	111.5 (113.3)	67.6	20.8	20.8	118.1	-	-	-	-
2 c	159.4 (159.6)	121.3 (120.1)	129.2 (128.5)	137.3 (137.8)	68.9	21.8	20.8	197.2	26.8	-	-	-
2 d	159.0 (159.0)	121.2 (119.9)	130.0 (130.1)	136.3 (138.1)	67.6	20.9	20.9	194.4	132.8	128.6	132.0	129.6
2 e	160.0 (158.9)	121.6 (119.6)	129.6 (127.9)	129.9 (130.0)	67.5	20.9	20.9	165.1	61.0	14.1	-	-
2 f	158.0 (158.1)	120.8 (119.8)	127.8 (127.3)	134.2 (127.3)	67.7	20.7	20.9	166.1	-	-	-	-
2 g	155.4	120.1	128.4	128.7	68.7	21.3	21.8	-	-	-	-	-

* (cal.) Carbon-13 chemical shift calculated using the substituent effect on the carbon-13 chemical shift of the phenyl piperidine N-oxide (2g).

** Taken from reference (4).

Table 3: Carbon-13 chemical shift assignment relative to TMS for O-(4-substituted phenyl) hydroxyl amines (3).

Compd. No.	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12
3 a*	164.6	113.8	125.8	141.5	56.9	25.4	23.3	-	-	-	-	-
3 b	163.1	114.6	133.9	104.2	56.9	25.3	23.3	119.8	-	-	-	-
3 c	163.0	113.6	130.6	130.9	56.9	25.4	23.3	197.1	26.2	-	-	-
3 d	163.2	113.5	128.2	132.6	56.9	25.4	24.0	195.7	138.6	129.8	131.8	130.8
3 e	161.3	113.7	131.3	131.8	56.8	25.5	23.3	167.1	60.4	14.5	-	-

* Taken from reference (4).

Table 4: The N-oxidation effect* on the carbon-13 chemical shift of N-(4-substituted phenyl) piperidine (1).

Compd. No.	$\Delta\delta$ C-1	$\Delta\delta$C-2	$\Delta\delta$C-3	$\Delta\delta$C-4	$\Delta\delta$C-5	$\Delta\delta$C-6	$\Delta\delta$C-7	$\Delta\delta$C-8	$\Delta\delta$C-9	$\Delta\delta$C-10	$\Delta\delta$C-11	$\Delta\delta$C-12
a	+6.1	+10.1	-1.5	+10.1	+20.8	-4.1	-2.3	-	-	-	-	-
b	+6.0	+ 8.5	-0.3	+12.8	+19.4	-4.4	-3.4	-2.1	-	-	-	-
c	+5.4	+ 8.3	-1.0	+10.5	+21.5	-5.1	-3.2	+2.0	+0.9	-	-	-
d	+5.2	+ 8.3	-1.2	+11.3	+19.8	-3.5	-2.5	+1.4	-6.3	+0.4	-0.1	+0.7
e	+5.4	+ 8.0	-1.6	+10.7	+18.6	-4.4	-3.5	-1.7	+0.8	-	-	-
f	+4.9	+ 7.3	-1.1	+11.4	+19.3	-3.5	-5.0	-1.7	-	-	-	-
g	+9.4	+ 5.4	-0.4	+10.5	+18.3	-4.5	-2.4	-	-	-	-	-

* $\Delta\delta$ C = δ C of the N-oxide (2) - δ C of the corresponding amine (1).

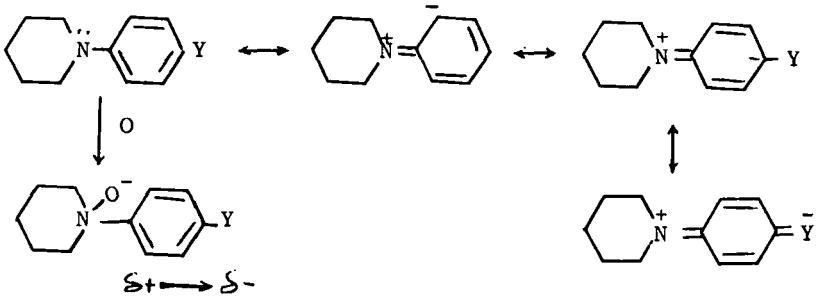
δ 122.5 (^1J = 170 Hz, ^2J = 2.5 Hz); C-3, δ 124.5 (^1J = 162 Hz, ^2J = 3 Hz), C-4, δ 147.9 (^1J = 4 Hz; ^3J = 6 Hz (meta coupling)). The same approach was followed in the assignments of aromatic ring carbon in the rearrangement products (3); (for 3a, C-2, δ 113.8 (^1J = 162 Hz, ^2J = 5 Hz); C-3, δ 125.8 (^1J = 165 Hz, ^2J = 6 Hz).

The carbon-13 chemical shifts for the heterocyclic SP^3 carbons (piperidine ring) were obtained using the previously reported[4,5] values for the heterocyclic saturated carbon atoms of the amines, the amine oxides and the rearrangement products.

The N-oxidation effect:

The N-oxidation of compounds (1a-g) to the corresponding N-oxides (2a-g) resulted in deshielding of C-1, C-2 and C-4 (Table 4). This deshielding is a result of the N-oxidation reaction which utilized the lone pair of the nitrogen of the amine by the oxygen of the N-oxide. The conversion of the amine to the N-oxide results in interruption of delocalisation of the amine nitrogen lone pair through the aromatic ring (Scheme 2), and so a deshielding is expected for ortho- and para-carbons. On the other hand the C-3 was somewhat unaffected by the N-oxidation with a small shielding (0.3 - 1.6 p.p.m.).

The heterocyclic ring carbon C-5 showed deshielding by (18.3 - 20.8 p.p.m.) as a result of the N-oxidation while C-6 and C-7 showed a shielding of (2.3 - 5.1 p.p.m.) (Table 4).



induced polarization only

(Scheme 2)

The N-oxidation effects and the correlation analysis:

It has been shown that various equations with one and two parameters can be successfully used for correlation of the para-substituent effect on the carbon-13 chemical shifts (C-p-SCS) of aromatic compounds[10], (e.g. equation 1).

In Hammett plots of substituent chemical shift (SCS) in the N-oxidation effect (SCS $\equiv \Delta\delta$ C-1) vs. σ_p and σ_m values the correlation coefficient (r) = 0.94 and 0.92 respectively. However, the use of a dual parameter σ°_R and σ_I (eq. 2) gives a better correlation (Figure);, r = 0.96

$$(\text{SCS} \equiv \Delta\delta \text{ C-1}) = 5.499 + 2.197\ \sigma_I \pm 0.31 + 5.693\ \sigma^{\circ}_R \pm 1.93 \quad \ldots(2).$$

The general predominant term (5.693 ρ_R) has been attributed to the effect of π-electron delocalization in amines as represented by scheme (2). The second term (2.197 ρ_I) is attributed to the effect of substituent induced polarization of the ring π-electrons. Therefore the substituent interacts in two mechanisms: resonance substituent effect mechanism and through-space transmission and polarization of the ring

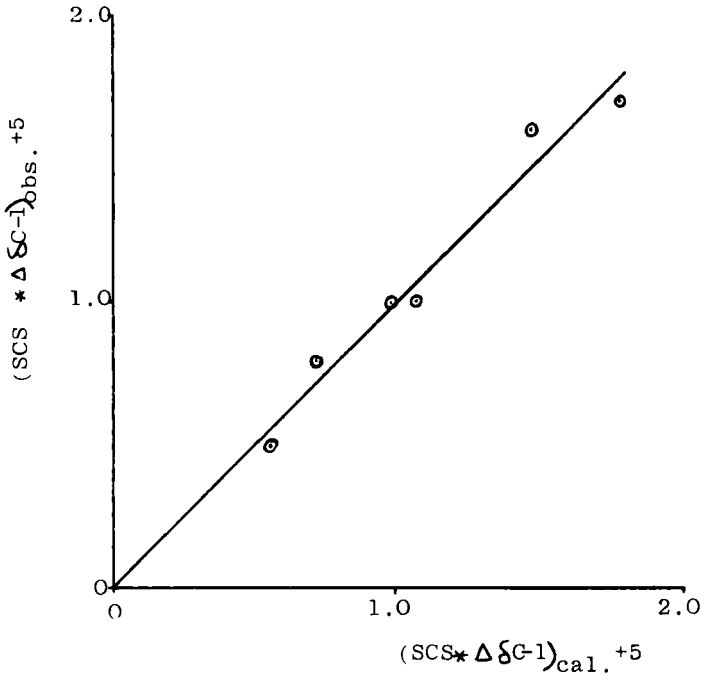


Fig. Plot of (SCS* C-1) observed VS. (SCS* C-1) calculated according to equation (2).

π-electrons with no net electron transfer between the substituent and the ring π-electrons (Scheme 2). The relative importance of factors operating in the N-oxidation effect can be estimated from the ratio $\frac{\rho_R}{\rho_I} = \frac{5.693}{2.197} = 2.6$.

The magnitude of the ratio means that resonance is always stronger than inductive effect at C-1 N-oxidation effect. The (SCS) in the N-oxidation effect on the aromatic C-2 (SCS *Δδ C-2) is found to be fairly correlated with the substituent constant σ_m (r = 0.9) whereas correlation with dual parameters

σ_I and σ°_R equation (3) produces only very slight improvement ($r = 0.91$).

$$(SCS * \Delta\delta\ C\text{-}2) = 0.566 + 4.459\ \sigma_I \pm 1.07 + 13.12\ \sigma^{\circ}_R \pm 6.72 \quad \ldots\ldots\ldots\ldots (3)$$

On the other hand poor correlation was found between the (SCS * $\Delta\delta$ C-3) and (SCS * $\Delta\delta$ C-4) and Hammett substituent constants.

EXPERIMENTAL:

Synthesis:

The tertiary amines were synthesized by nucleophilic substitution of piperidine with 4-substituted fluorobenzene in dimethyl sulphoxide. The N-oxides were prepared by oxidation of the tertiary amines with performic acid (a mixture of 98 % formic acid and 30 % hydrogen peroxide). Rearrangement of the tertiary amine N-oxides was performed by heating the free base in dioxane for 3 hrs. The products were purified by column chromatography with neutral alumina. The preparative details of these compounds are reported in reference (2).

Carbon-13 NMR Spectra:

Proton decoupled and coupled spectra were obtained on a Bruker WH 90 DS spectrometer equipped with an Aspect 2000, 32k computer operating at 22.63MHz for ^{13}C NMR with internal deuterium lock. The spectral width was 6024 Hz; a flip angle of 45° was used and the free induction decay was accumulated in 8k, and the frequency domain spectra obtained in 4k, data

points. Samples were dissolved in $CDCL_3$ 10 - 15 % by V/V or W/V in a 10 mm O.D. Wilmad tube and a few drops of TMS were added as internal reference.

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11. $(SCS \neq \Delta\delta C) = (\Delta\delta C \quad Y \neq H) - (\Delta\delta C \quad Y = H)$.

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