MAGNETIC RESONANCE IN CHEMISTRY, VOL. 36, 296–299 (1998)

Note

Carbon-13 NMR Spectra of Imidazole 1-Oxides. Comparison with the Parent Imidazoles

J. Alcázar,[1] A. de la Hoz[1]* and M. Begtrup[2]

[1] Facultad de Química, Universidad de Castilla-La Mancha, E-13071 Ciudad Real, Spain
[2] Department of Medicinal Chemistry, Royal Danish School for Pharmacy, DK-2100 Copenhagen, Denmark

Received 23 June 1997; revised 10 September 1997; accepted 26 September 1997

ABSTRACT: The ^{13}C chemical shifts and C–H coupling constants of a series of imidazole 1-oxides were compared with those of the parent imidazoles and imidazolium salts in order to show the influence of *N*-oxidation on these parameters. The ^{13}C chemical shifts can be related to the electron density at the carbon atoms whereas long range C–H coupling constants can be related to the relative localization or delocalization of the π system in imidazoles, imidazolium salts and imidazole *N*-oxides.

KEYWORDS: NMR; ^{13}C NMR: imidazole 1-oxides

INTRODUCTION

In this work, a comparison was made of the ^{13}C chemical shifts and C–H coupling constants of imidazole-1-oxides and the parent imidazoles, in order to investigate the influence of *N*-oxidation on these parameters.

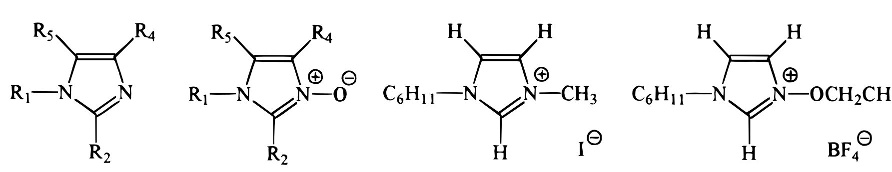
RESULTS

The ^{13}C chemical shifts and C–H coupling constants of some representative imidazole 1-oxides (**2**) and a comparison with the data of the corresponding parent imidazoles (**1**) and imidazolium salts (**3i** and **4i**) (Fig. 1) are given in Tables 1–4.

Signal assignment

The carbon signals of the imidazole 1-oxides were assigned from the signal splitting caused by long-range C–H couplings. For example, in **2i**, the C-2 signal displays a quartet fine structure with similar coupling constants due to coupling with H-4, H-5 and H-1′. C-5 appears as a double double doublet with different coupling constants due to coupling with H-2, H-4 and H-1′. C-4 appears as a double doublet with different coupling constants due to coupling with H-2 and H-5. For the assignment of the *p*-tolylimidazole 1-oxides the mono- and disubstituted methyl derivatives can be used, by comparing the effect of the individual methyl group on the chemical shifts.

When two or three methyl groups were present, signals from methyl groups at C-4 and C-5 were distinguished by comparison with the isomeric 4- and 5-methyl compounds **c** and **d**. Methyl groups at C-2, in **1f** and **2f**, were identified by their larger one-bond C–H coupling constants. When these criteria gave ambiguous results or could not be used owing to coalescent signals as in **2f**, identification was confirmed by one-bond C–H correlation experiments.



1a-j **2a-j** **3i** **4i**

a; R_1=p-CH_3-C_6H_4, R_2=R_4=R_5=H
b; R_1=p-CH_3-C_6H_4, R_2=CH_3, R_4=R_5=H
c; R_1=p-CH_3-C_6H_4, R_2=R_5=H, R_4=CH_3
d; R_1=p-CH_3-C_6H_4, R_2=R_4=H, R_5=CH_3
e; R_1=p-CH_3-C_6H_4, R_2=H, R_4=R_5=CH_3
f; R_1=p-CH_3-C_6H_4, R_2=R_4=R_5=CH_3
g; R_1=p-CH_3-C_6H_4, R_2=$CH_2C_6H_5$, R_4=R_5=CH_3
h; R_1=p-CH_3-C_6H_4, R_2=C_6H_5, R_4=R_5=CH_3
i; R_1=C_6H_{11}, R_2=R_4=R_5=H
j; R_1=C_6H_{11}, R_2=$CH_2C_6H_5$, R_4=R_5=H

Figure 1

---

* *Correspondence to*: A. de la Hoz, Facultad de Química, Universidad de Castilla-La Mancha, E-13071 Ciudad Real, Spain.
E-mail: adlh@qino-cr.uclm.es

Contract/grant sponsor: Lundbeck Foundation.
Contract/grant sponsor: Danish Council for Technical and Scientific Research.
Contract/grant sponsor: Spanish DGICyT; *contract/grant number*: PB94-0742.

CCC 0749-1581/98/040296–04 $17.50

Table 1. ^{13}C NMR chemical shifts (ppm relative to $CDCl_3$ at δ 76.9 ppm) of 1, 2, 3i and 4i, with deuterochloroform as solvent

Compound	C-2	C-4	C-5	C-1′	C-2′	C-3′	C-4′	$R_{4'}$	R_2	R_4	R_5
1a	135.5	130.1	118.3	134.9	121.3	130.3	137.4	20.9	—	—	—
2a	125.8	123.4	115.7	133.6	121.1	130.9	139.2	21.2	—	—	—
2b	134.6	121.4	115.6	133.8	125.0	130.5	139.6	21.1	8.8	—	—
1c	134.6	139.3	114.7	135.1	121.0	130.2	136.9	20.9	—	13.7	—
2c	124.1	131.5	112.2	133.7	120.4	130.6	138.2	20.9	—	8.0	—
2d	125.8	120.3	126.1	131.7	125.5	130.3	139.8	21.0	—	—	9.8
1e	134.9	134.0	122.7	134.3	125.2	129.8	137.8	20.9	—	12.7	8.9
2e	124.4	127.0	121.5	132.1	125.5	130.3	139.4	21.0	—	7.3	9.3
1f	142.8	131.3	123.1	134.5	127.1	130.0	138.3	21.1	13.7	12.5	9.3
2f	132.5	124.7	119.5	131.5	126.9	130.1	139.4	20.8	8.5	7.1	8.8
2g	134.6	125.2	120.0	131.7	127.6	130.0	139.6	21.1	28.6[a]	7.4	9.0
1h	145.1	130.7	125.4	135.2	127.9	130.1	138.3	21.2	—[a]	12.7	9.6
2h	134.0	124.0	121.9	132.6	127.6	130.3	139.4	21.1	—[a]	7.6	9.5
1i	135.3	128.8	116.9	56.8	34.4	25.4	25.2	—	—	—	—
2i	124.7	121.8	114.3	58.7	33.7	25.0	24.8	—	—	—	—
3i[b]	135.4	123.5	120.3	59.9	33.3	24.7	24.4	—	—	—	—
4i[c]	131.0	119.4	118.3	61.0	33.0	24.8	24.4	—	—	—	—
2j	136.4	120.5	112.1	57.0	33.1	25.2	24.5	—	27.8[a]	—	—

[a] Phenyl group signals are given in Table 2.
[b] R-3; CH_3, 37.0.
[c] R-3; CH_3, 13.0; CH_2, 79.2.

The signals from the cyclohexyl group were assigned assuming that shielding decreases when the number of bonds from the imidazole ring increases.

The assignment of the signals from *N*-tolyl groups was based on data from the literature[1,2] invoking the effect of the 4′-methyl group on the chemical shifts of the *N*-phenyl derivatives[3] and the multiplicity in the coupled spectra. Signals from *C*-phenyl groups were assigned from the coupled spectra considering the multiplicity which resulted from long-range coupling constants.[2]

Carbon chemical shifts

Quaternization of imidazoles **1** to the imidazolium salts **3** and **4** leads to low-field shifts of all the imidazole carbon signals except that of C-4, which is shielded probably by the steric compression produced by quaternization.[4,5] In constrast, oxidation of imidazoles **1** to imidazole 1-oxides **2** results in a high-field shift of all the imidazole carbon signals (mean values 10.4 ppm for C-2, 7.0 ppm for C-4 and 2.7 ppm for C-5). Shielding is also observed for lateral carbon atoms (5.2 for 2-CH_3 and 5.1–5.7 for 4-CH_3) with the exception of 5-CH_3.

Table 2. ^{13}C NMR chemical shifts (ppm relative to $CDCl_3$ at δ 76.9 ppm) of phenyl substituents at position 2

Compound	C-1″	C-2″	C-3″	C-4″
2g	136.4	128.4	128.2	126.4
1h	133.2	128.0	127.6	127.5
2h	126.5	129.1	128.8	128.7
2j	135.0	128.0	128.8	127.1

These high-field shifts can be explained by the increased negative charge accumulated at the carbon atoms of the *N*-oxides **2** as reflected by the resonance structures **III**–**V** (Fig. 2).[6] The shielding may reflect the observation that the relative contribution of these resonance structures to the hybrid decreases in the order **III** > **IV** > **V**. These features run parallel with the shift displacements observed when pyridines are alkylated to give pyridinium salts or oxidized to pyridine-1-oxides.[7]

In accordance with the relative contribution of the three resonance structures to the hybrid, α-carbon atoms of substituents at positions 2 and 4 are influenced more than those at position 5, which are hardly affected at all.

In phenyl-substituted azoles the shift difference between C-3′ and C-2′ reflects the extent of conjugation between the phenyl and the azole rings.[8] This shift difference remains almost unchanged, δ(C-3′) − δ(C-2′) = 9.8 and 10.2 ppm, upon *N*-oxidation of the 1-*p*-tolylimidazoles **1a** and **1c** respectively, indicating that *N*-oxidation does not affect the conjugation between the

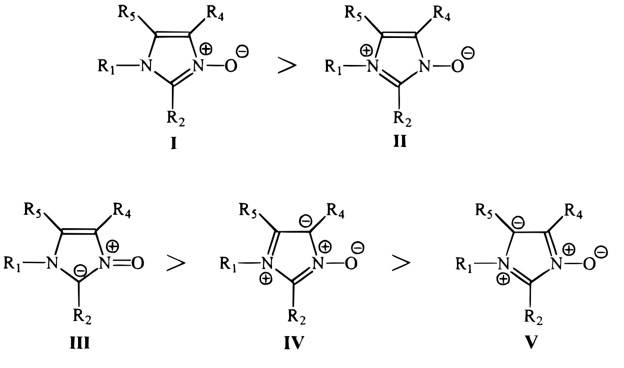


Figure 2

Table 3. ^1J(CH), ^2J(CH) and ^3J(CH) values (Hz) for **1**, **2**, **3i** and **4i**

Compound	Parameter	C-2	C-4	C-5	C-1′	C-2′	C-3′	C-4′	$R_{4'}$	R_2	R_4	R_5
1a	^1J	208.7	189.9	190.3		161.7	159.2		127.3			
	^2J		10.5	16.6				6.0				
	^3J	10.4/6.4	10.5	3.0			5.0	4.0	2.3			
2a	^1J	219.1	200.9	198		162.2	160.8		127.0			
	^2J		10.6	12.1								
	^3J	4.0/4.0	5.5	5.1	7.3	4.0	5.0					
2b	^1J		200.4	198.1		161.9	160.6		127.1			
	^2J		10.5	11.8				6.5				
	^3J				7.0	5.3	7.0/5.0	6.5	4.3			
1c	^1J	207.3		188.2		161.0	159.2		126.6		126.9	
	^2J											
	^3J	6.8		4.0		3.6	5.0		4.1			
2c	^1J	218.5		196.0		160.0	162.1		126.9		131.3	
	^2J							6.0				
	^3J	2.8		4.5	6.8	3.4	5.0	6.0	4.1			
2d	^1J	219.8	193.8			162.5	160.7		127.0			130.1
	^2J							6.6				
	^3J				10.1	5.2	6.6/5.0	6.6	4.3			
1e	^1J	207.5				160.9	159.4		126.5		126.4	127.9
	^2J							6.3				
	^3J				9.2	5.6	6.9/5.0	6.3	4.1			
2e	^1J	218.6				162.2	160.4		127.0		129.6	129.6
	^2J							6.6				
	^3J				10.0	5.0	6.8/5.1	6.6	4.3			
1f	^1J					161.5	159.7		126.7	128.4	126.1	127.7
	^2J	7.0						6.3				
	^3J				8.6	5.1	5.9/4.9	6.3	4.6			
2f	^1J					163.7	159.2		126.9	131.4	129.3	129.3
	^2J	7.7						6.6				
	^3J				9.5	5.5	8.6/5.6	6.6	4.5			
2g	^1J					161.2	159.1		130.4	130.4[a]	129.2	129.1
	^2J	8		6.6				7.0				
	^3J			4.6	9.1	5.0	7.4/5.0	7.0	4.5	4.5		
1h	^1J					160.5	159.1		126.3	—[a]	126.4	128.1
	^2J							6.4				
	^3J	4.0			9.9		6.8/5.3	6.4	4.3			
2h	^1J					162.6	161.0		126.9	—[a]	129.8	129.6
	^2J							6.5				
	^3J	3.1			9.3	5.0	5.4	6.5	4.3			
1i	^1J	207.4	188.4	188.4	144.5	129.4	127.7	127.7				
	^2J		10.4	13.1								
	^3J		10.4	3.5								
2i	^1J	216.5	199.4	195.7	141	127.7	127.7	127.7				
	^2J		10.5	11.7								
	^3J	3.5	5.5	5.5/3.5								
3i[b]	^1J	220.1	201.8	200.9	143.5	128.9	129.9	132.6				
	^2J		11.1	11.2								
	^3J	4.2	5.5/3.3	5.4/3.8								
4i[c]	^1J	225.9	207.5	204.5	144.0	127.5	128.7	124.4				
	^2J		11.1	9.8								
	^3J	3.9	4.5	6.0/3.5								
2j	^1J		201.2	196.6	137.0	127.7	126.5	125.9		131.0[a]		
	^2J		10.3	11.3								
	^3J			4.5								

[a] Phenyl group, in Table 4.

[b] R-3; CH_3, ^1J, 144.0.

[c] R-3; CH_3, ^1J, 128.1; ^2J, 2.7; CH_2, ^{1}J, 150.3; ^2J, 4.5.

Table 4. ^1J(CH), ^2J(CH) and ^3J(CH) values (Hz) of phenyl substituents in position 2

Compound	Parameter	C-1″	C-2″	C-3″	C-4″
2g	^1J		151.3	159.6	152.6
	^2J	6.9			
	^3J	6.9	7.3	7.0	7.5
1h	^1J		163.9	161.7	160.1
	^2J			5.6	6.7
2h	^1J		162.6	160.4	161.1
	^3J	6.7	7.1	7.3/5.4	7.6
2i	^1J		157.6	160.4	160.8
	^2J	6.8			
	^3J	6.8		7.3	6.9

tolyl group and the imidazole ring. If, however, a substituent is introduced at C-2 or C-5 in the imidazole 1-oxides **1**, the shift difference between C-3′ and C-2′ is reduced to 5.5 ppm in **2b** and 4.8 ppm in **2d** and **2e** and drops further to 3.2, 2.4 and 2.7 ppm when substituents are present at both C-2 and C-5 in **2f**, **2g** and **2h**, respectively. This shows that substituents at C-2 and C-5 impede conjugation between the two rings by increasing the torsional angle between the rings.

Alkylation of imidazole *N*-oxide **2i** with triethyloxonium tetrafluoroborate gives the 1-ethoxyimidazolium tetrafluoroborate **4i**. The carbon chemical shifts of this compound are more like those of the imidazolium salts **3i** than those of the *N*-oxides **2** in that the C-2 signal displays a high-field shift whereas the C-4 and C-5 signals are not displaced in comparison with the parent imidazole **1**. This result confirms that the resonance structures **III**–**V**, which are insignificant in **4i**, are responsible for the observed shift effects in the imidazole 1-oxides.

C–H coupling constants

N-Oxidation leads to a significant increase in the one-bond C–H coupling constants. The increase is even higher in the imidazolium salts including **3i** and **4i** (compare **1i**, **2i**, **3i**, and **4i** in Table 3). This increase reflects the lower electron density of the imidazole ring.

Long-range coupling constants signify that the heterocyclic bonds are more delocalized in the imidazole 1-oxides **2** than in the parent imidazoles **1**. For instance, in **1a** ^3J(C2, H4) = 10.4 Hz and ^3J(C4, H2) = 10.5 Hz are larger than ^3J(C2, H5) = 6.4 Hz and ^3J(C5, H2) = 3.0 Hz, indicating that the double bond is localized at C2—N3.[2] In the *N*-oxide **2a**, these coupling constants are very similar ^3J(C2, H4) = 4.0 Hz, ^3J(C4, H2) = 5.5 Hz, ^3J(C2, H5) = 4.0 Hz, ^3J(C5, H2) = 5.1 Hz, showing that the double bond is delocalized over N1—C2—N3.

EXPERIMENTAL

^{13}C NMR spectra were recorded at 75.415 MHz with a 90° pulse and a digital resolution of 0.5 Hz on a Varian Unity 300 instrument. Heteronuclear correlation experiments were performed using the standard Varian software. C–H coupling constants were determined by inspection of the signal splitting.

Imidazole 1-oxides **2** were prepared by reaction of 1,2-diimines with oximes as described previously.[9] Imidazoles **1** were obtained by deoxygenation of the corresponding *N*-oxides.[10] Imidazoles **1b**, **1d**, **1g** and **1j** were not prepared as the *N*-oxides were available in very small quantities. 3-Methyl-1-cyclohexylimidazolium iodide (**3i**) was obtained as a yellow oil by reaction of 3-cyclohexylimidazole (**1i**) with methyl iodide in chloroform solution at room temperature for 48 h followed by evaporation of the solvent. 3-Cyclohexyl-1-ethoxyimidazolium tetrafluoroborate (**4i**) was obtained as a colourless oil by treatment of 3-cyclohexylimidazole 1-oxide (**2i**) with triethyloxonium tetrafluoroborate followed by removal of the solvent and column chromatography on silica gel [eluent, ethyl acetate–methanol (1 : 1)].[9]

In order to avoid confusion with different numbering in imidazoles **1** and imidazole 1-oxides **2**, the numbering was based on that of the parent imidazole in both series (Fig. 1). Atom substituents are numbered using primes and double primes, giving the atom closest to the imidazole ring the lowest number.

Acknowledgements

Thanks are due to the Lundbeck Foundation, the Danish Council for Technical and Scientific Research and the Spanish DGICyT (project PB94-0742).

REFERENCES

1. M. Begtrup, *Acta Chem. Scand.* **27**, 3101 (1973).
2. E. Breitmaier and W. Voelter, *Carbon-13 NMR Spectroscopy. High Resolution, Methods, and Applications in Organic Chemistry and Biochemistry*, 3rd ed. VCH, Weinheim (1987).
3. E. Pretsch, T. Clerc, J. Seibl, W. Simon, *Tabellen zur Struckturaufklärung Organischer Verbindungen mit Spektroskopischen Methoden.* Springer, New York (1976).
4. R. M. Claramunt and J. Elguero, *An. Quim.* **82**, 162 (1986).
5. F. Benedini, F. Ferrario and A. Sala, *Magn. Reson. Chem.* **30**, 1137 (1992).
6. M. Begtrup, *Heterocycles* **33**, 1129 (1992).
7. A. J. Boulton and A. McKillop, in *Comprehensive Heterocyclic Chemistry*, edited by A. R. Katritzky, Vol. 2. Pergamon Press, Oxford (1984).
8. M. Begtrup, *Acta Chem. Scand.* **28**, 61 (1974).
9. J. Alcázar, M. Begtrup and A. de la Hoz, *J. Chem. Soc., Perkin Trans. 1* 2467 (1995).
10. J. Alcázar, M. Begtrup and A. de la Hoz, unpublished results.