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Characterization of 2-aryl-1,3,4-oxadiazoles by ^{15}N and ^{13}C NMR spectroscopy

Barbara Nowak-Wydra, Błażej Gierczyk and Grzegorz Schroeder*

Faculty of Chemistry, Adam Mickiewicz University, Grunwaldzka 6, PL-60 780 Poznań, Poland

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^{15}N NMR chemical shifts of 2-aryl-1,3,4-oxadiazoles were assigned on the basis of the $^{1}H-^{15}N$ HMBC experiment. Chemical shifts of the nitrogen and carbon atoms in the oxadiazole ring correlate with the Hammett σ-constants of substituents in the aryl ring ($r^2 \geqslant 0.966$ for N atoms). ^{15}N NMR data are a suitable and sensitive means for characterizing long-range electronic substituent effects. Additionally, ^{13}C NMR data for these compounds are presented. Copyright © 2003 John Wiley & Sons, Ltd.

KEYWORDS: NMR; ^{15}N NMR; ^{13}C NMR; chemical shifts; Hammett correlations; 1,3,4-oxadiazole

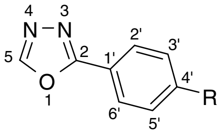
INTRODUCTION

Correlations between NMR chemical shifts and structure are an important aspect of modern spectroscopy. As a continuation of our investigations in this area,[1–3] we now present an ^{15}N NMR study of a series of *para*-substituted 2-phenyl-1,3,4-oxadiazoles and a correlation of the nitrogen and carbon chemical shifts with Hammett σ-values of substituents in the aryl ring.

The 1,3,4-isomers are the most extensively studied oxadiazoles, because of their interesting electro-optical, electronic[4,5] and biological activities.[4–8] The wide use of these compounds in medicine, agriculture and industry has stimulated investigations of their chemical properties.

Although the ^{1}H and ^{13}C NMR spectra of some disubstituted 1,3,4-oxadiazoles have already been published,[9–11] there has been no systematic study of their ^{15}N NMR chemical shifts, which may be useful in predicting the mechanism of their activity. To the best of our knowledge, only one paper has reported the ^{15}N NMR chemical shifts for unsubstituted 1,3,4-oxadiazole.[12]

Figure 1 shows the structure of the oxadiazoles studied and the numbering of atoms.



	1a	1b	1c	1d	1e	1f	1g	1h	1i	1j
R	NMe_2	NH_2	OMe	Me	H	Ph	F	Br	CN	NO_2

Figure 1. The 2-aryl-1,3,4-oxadiazoles studied.

EXPERIMENTAL

Synthesis

The compounds were prepared according to a modified procedure described in the literature.[13]

To a solution of the corresponding benzoic acid (0.01 mol) in anhydrous methanol (25 cm^3), freshly distilled thionyl chloride (0.015 mol) was added dropwise over 1 h with stirring. The solvent was evaporated and the ester formed was used in the next step without purification. In the case of cyanobenzoic acid, sulfuric acid was used (0.25 cm^3) instead of $SOCl_2$ and the solution was heated for 10 h.

To the crude ester, hydrazine hydrate (0.025 mol) was added and this mixture was kept at room temperature until a precipitate of acyl hydrazide was formed. The crystals were filtered off and dried in vacuum.

The hydrazide was heated in trimethyl orthoformate for 10 h under reflux, then the solvent was evaporated and the oily residue was distilled in vacuum. The product that crystallized in the condenser was recrystallized from acetone and hexane.

NMR spectra

The NMR spectra were recorded at 298 K on a Bruker Avance DRX 600 spectrometer operating at frequencies of 600.055 MHz (^{1}H), 150.899 MHz (^{13}C) and 60.821 MHz (^{15}N) and equipped with a 5 mm triple-resonance inverse probehead {$^{1}H/^{31}P$/BB} with a self-shielded z-gradient coil (90° ^{1}H pulse width 9.0 µs, ^{13}C pulse width 13.3 µs and ^{15}N pulse width 19 µs).

Spectra were measured in $CDCl_3$ and the sample concentrations ranged from 10 to 60 mg per 600 µl of solvent. Chemical shifts δ (ppm) were referenced to internal Me_4Si for ^{1}H and ^{13}C. The ^{15}N NMR chemical shifts were referenced to the signal of external CH_3NO_2 in a 1 mm diameter capillary inserted coaxially in the 5 mm NMR tube.

Two-dimensional ^{1}H, ^{13}C gradient selected HSQC (heteronuclear single quantum coherence) and ^{1}H, ^{13}C and ^{1}H,

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*Correspondence to: Grzegorz Schroeder, Faculty of Chemistry, Adam Mickiewicz University, Grunwaldzka 6, PL-60 780 Poznań, Poland. E-mail: schroede@amu.edu.pl

^{15}N gradient selected HMBC (heteronuclear multiple bond coherence) experiments were performed using standard pulse sequences from the Bruker pulse-sequence library. In ^{1}H, ^{15}N HMBC measurements the delays for evolution of multiple-bond couplings were set to 55–280 ms, which correspond to 2–9 Hz coupling constant values. The ^{1}H spectral windows were used depending on the case and 1024 data points along the t_2-axis were collected and then zero-filled to 2048 points prior to Fourier transformation (FT); 32–128 scans for 512 t_1 time increments were collected and zero-filled to 1024 prior to FT. The chemical shift measurement accuracy was better than 0.05 ppm.

RESULTS AND DISCUSSION

For the synthesized series of 2-aryl-1,3,4-oxadiazoles (**1a–j**), the ^{15}N chemical shift data are summarized in Table 1. The assignments of N-3 and N-4 chemical shifts were made on the basis of the two-dimensional ^{1}H, ^{15}N correlation HMBC spectra.

In the ^{1}H, ^{15}N HMBC spectra both nitrogen atoms, N-3 and N-4, correlate with H-5 (via three and two bonds, respectively) and can be distinguished by correlation of N-3 with H-2′,6′ (via four bonds), whereas that of N-4 with H-2′,6′ is not observed (separation by five bonds). For the N-4 atom $^{2}J(^{15}N,^{1}H)$ was observed, and its values, ca 10.5–11.0 Hz, do not depend on substituent electronegativity.

An examination of the data in Table 1 shows that the chemical shifts of both nitrogen atoms depend on the electronic properties of the aryl substituent; the electron-withdrawing groups cause high-wavenumber shifts, whereas electron-donating groups cause low-wavenumber shifts. The range of chemical shifts for N-3 for the studied compounds is 18.07 ppm (from −96.28 to −78.21 ppm), whereas that for N-4 is only 5.18 ppm (from −75.21 to −70.24 ppm) and shows that changes in electron density for N-3 under the influence of substituents in the aryl ring are larger than those for N-4.

The protonated carbons could be assigned using correlation via one-bond coupling observed in the ^{1}H, ^{13}C HMQC spectra. The quaternary carbons were distinguished on the basis of ^{1}H, ^{13}C HMBC measurements. The C-2 atom shows a strong coupling via three bonds with H-2′,6′ protons of the aryl substituent and correlation via four bonds with H-5 (strong) and H-3′,5′ (weak, not for all compounds observed). The C-2 chemical shift is very characteristic (ca 165 ppm), typical for quaternary sp^2 carbon, bonded to one oxygen and one nitrogen atom. The non-protonated carbons of aryl substituents could be distinguished on the basis of couplings with H-2′,6′ and H-3′,5′ protons. C-1′ shows coupling to H-3′,5′ only (via three bonds) and the correlation via two bonds, to H-2′,6′ protons, is not observed in all cases. In contrast, C-4′ correlates with H-2′,6′ only. In the case of proton-containing substituents in the aryl ring, C-4′ also shows a coupling to the substituent protons.

Table 2 shows the ^{13}C NMR chemical shifts for **1a–j**. The chemical shift ranges for the carbon atoms of the oxadiazole ring, C-2 and C-5, are very small, 2.38 and 3.55 ppm, respectively.

Chemical shifts were correlated with single Hammett σ-constants (σ_p) or inductive (σ_I) and resonance (σ_R) Hammett values determined for the substituents in the aryl ring. Correlation equations for regression coefficients using single Hammett σ-constants and both inductive and resonance parameters, respectively, are the following: chemical shift $= \rho\sigma_p +$ intercept and chemical shift $= \rho_I\sigma_I + \rho_R\sigma_R +$ intercept. Chemical shift values of 10 compounds were used in correlation studies.

Statistical data for Hammett analysis of chemical shifts of some carbon and nitrogen atoms in **1a–j** are summarized in Table 3. Linear correlations between chemical shifts and Hammett values of substituents in the aryl ring were obtained for both nitrogen atoms N-3 and N-4 with the classical σ_p substituent constants ($r^2 \geqslant 0.966$). The N-3 atom in the 1,3,4-oxadiazole ring is about four times more

Table 1. Hammett values (σ_i) for aryl substituents and ^{15}N NMR chemical shifts for **1a–j**

Compound	R	σ_p[a]	σ_I[a]	σ_R[a]	N-3	N-4	Other N-atoms
1a	NMe_2	−0.63	0.06	−0.55	−96.28	−75.06	−328.27[b]
1b	NH_2	−0.57	0.12	−0.5	−94.66	−75.17	−321.41[c]
1c	OMe	−0.28	0.27	−0.42	−91.83	−74.89	
1d	Me	−0.14	−0.05	−0.13	−88.57	−73.67	
1e	H	0	0	0	−86.77	−73.44	
1f	Ph	0.05	0.1	−0.1	−86.15	−72.71	
1g	F	0.15	0.5	−0.31	−86.94	−72.94	
1h	Br	0.26	0.44	−0.16	−84.64	−72.39	
1i	CN	0.70	0.56	0.08	−79.00	−70.90	−122.27[d]
1j	NO_2	0.81	0.65	0.15	−78.21	−70.24	14.72[e]

[a] Ref. 14.
[b] $\underline{N}(CH_3)_2$.
[c] $\underline{N}H_2$.
[d] $C\underline{N}$.
[e] $\underline{N}O_2$.

Table 2. ^{13}C NMR chemical shifts for **1a–j**

Compound	C-2	C-5	C-1′	C-2′,6′	C-3′,5′	C-4′	Other C-atoms
1a	165.72	152.04	110.78	128.99	111.88	152.89	40.67[a]
1b	165.05	150.07	113.31	128.97	114.75	164.97	
1c	164.50	152.13	115.87	128.87	114.09	162.35	55.53[b]
1d	165.55	153.03	121.38	127.46	130.29	143.06	20.01[c]
1e	164.71	152.73	123.36	127.01	129.02	131.94	
1f	165.09	152.92	122.65	127.90	128.11	145.38	140.21[d] 127.65[e] 129.38[f] 128.64[g]
1g	163.69	152.57	119.62	129.17	116.24	164.65	
1h	164.55	153.21	127.19	129.05	133.04	122.90	
1i	163.33	153.23	127.40	127.64	132.96	115.60	117.74[h]
1j	163.48	153.89	129.23	128.36	124.82	150.27	

[a] $N(\underline{C}H_3)_2$.
[b] $O\underline{C}H_3$.
[c] $\underline{C}H_3$.
[d] $\underline{C}$-1″.
[e] $\underline{C}$-2″,6″.
[f] $\underline{C}$-3″,5″.
[g] $\underline{C}$-4′.
[h] $\underline{C}N$.

Table 3. Statistical data for correlation between the chemical shifts and Hammett parameters of carbon and nitrogen atoms in **1a–j**[a]

Probe atom	$\rho \pm s_\rho$	Substituent constant	$i \pm s_i$	n	r^2
N-3	12.35 ± 0.55	σ_p	-87.74 ± 0.25	10	0.984
N-3	ρ_I: $9{,}06 \pm 0.95$ ρ_R: $18{,}96 \pm 1.00$	σ_I and σ_R	-86.03 ± 0.43	10	0.990
N-4	3.47 ± 0.23	σ_p	-73.26 ± 0.10	10	0.966
N-4	ρ_I: 2.97 ± 0.56 ρ_R: 4.02 ± 0.59	σ_I and σ_R	-72.97 ± 0.25	10	0.958
C-2	-1.45 ± 0.35	σ_p	164.62 ± 0.16	10	0.686
C-2	ρ_I: -2.68 ± 0.50 ρ_R: -0.80 ± 0.52	σ_I and σ_R	165.12 ± 0.23	10	0.865
C-5	1.72 ± 0.47	σ_p	152.52 ± 0.21	10	0.629
C-5	ρ_I: 0.58 ± 0.99 ρ_R: 3.16 ± 1.04	σ_I and σ_R	153.04 ± 0.45	10	0.652
C-1′	12.12 ± 1.68	σ_p	120.65 ± 0.76	10	0.866
C-1′	ρ_I: 5.46 ± 2.77 ρ_R: 21.77 ± 2.90	σ_I and σ_R	123.85 ± 1.25	10	0.924

[a] ρ = regression coefficient for the single parameter; i = intercept; s_ρ and s_i = standard deviations; n = number of points; r = correlation coefficient.

sensitive to the electronic effects of substituents in the aryl ring than N-4 ($\rho = 12.35$ and 3.47 for N-3 and N-4, respectively).

Carbon C-5 shows the expected electron density variations, whereas in the case of C-2 a reverse substituent effect is observed (electron-withdrawing substituents promote low-wavenumber shifts and vice versa).

For both carbon atoms of the oxadiazole ring, no correlation between the ^{13}C chemical shifts and Hammett parameter was found. In the case of C-2, a dissection of the substituent effect into its inductive and resonance components, σ_I and σ_R, improves the correlation coefficient slightly and shows that inductive effects of the substituent are predominant. This can be explained by the redistribution of electron density due to the polarization of the C=N double bond, as described previously.[15,16]

As a result of this study, we can conclude that (i) substituents in the aryl ring of the compounds studied are able to exert long-range electronic effects, affecting the chemical shifts of both the N-3 and N-4 atoms in the

1,3,4-oxadiazole ring; (ii) ^{15}N NMR chemical shift data for 2-aryl-1,3,4-oxadiazoles, reflecting the π-electron density in the oxadiazole ring, provide further insight into the structural features which determine their biological and optoelectronic activity.

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