SHORT PAPER

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NMR evidence for cationic behaviour of the benzotriazole ring in novel α-(benzotriazol-1-yl)-N-acylglycines

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Spin coupling of a proton to a nitrogen in the benzotriazole ring of novel α-(benzotriazol-1-yl)-N-acylglycines **1–3** revealed the zwitterionic properties of these compounds.

Keywords: benzotriazole ring, α-(benzotriazol-1-yl)-N-acylglycines

Benzotriazole is a synthetic auxiliary which depending on the nature of the attached groups and the reaction conditions can exist as both cationic or anionic species.[1]

In the course of our investigations on the structure–activity relationship of cholecystokinin antagonists, novel acylglycine compounds **1–3** were prepared by condensation of benzotriazole, glyoxylic acid and aromatic amides with the azeotropic removal of water[2] (Scheme 1).

The ^1H NMR of these compounds showed a triplet with coupling constant of 51.2 Hz and chemical shift around 7.2 ppm corresponding to one proton which was exchangeable with D_2O (Fig.1).

Based on these observations it was reasoned that in ([$^2H_6$] DMSO) that was used as the solvent for ^1H NMR spectroscopy, acylglycine compounds **1–3** may behave as zwitterions in which the benzotriazole moiety accepts the proton resulting from the ionisation of the carboxyl group (Scheme 1) and the indicating triplet arises from the spin coupling of the ^{14}N nucleus to a proton.

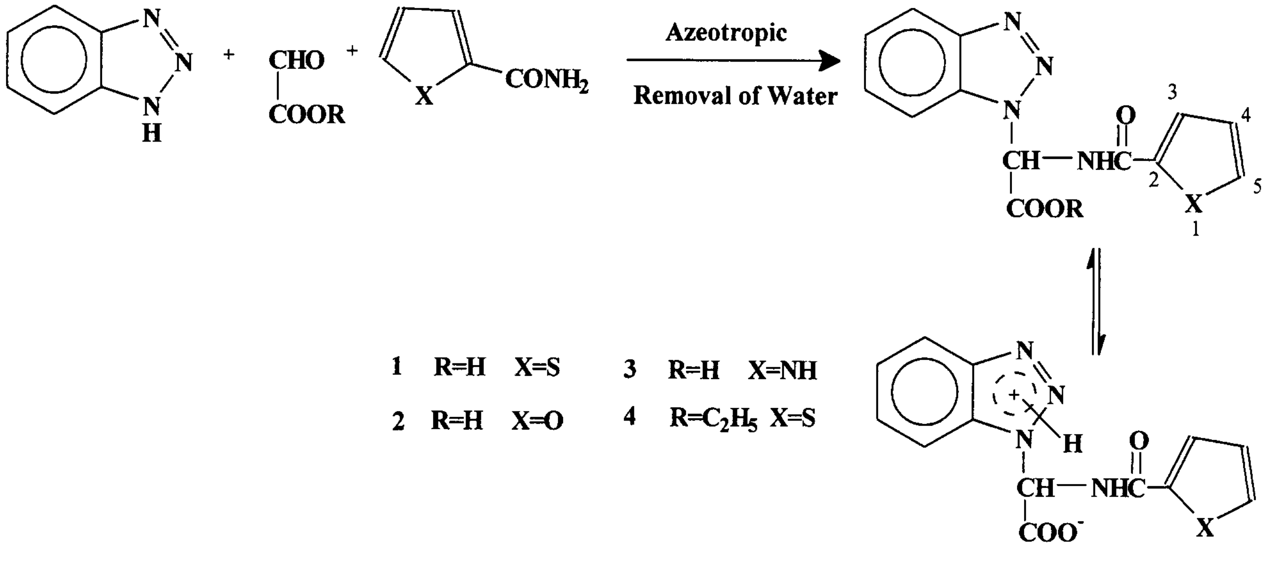
Consistent with our interpretation the triplet resulting from ^{14}N–^1H spin coupling was absent in ^1H NMR spectrum of the ethyl ester of compound **1** which cannot exist in zwitterionic form.

Spin coupling between ^{14}N and ^1H nuclei is not usually observable because of the rapid quadrupolar relaxation of the ^{14}N nucleus.[3] However, this pattern of coupling has been reported in spectra of completely anhydrous ammonia,[4,5] ammonium ions in acid solutions,[6] anhydrous dimethylamine,[7] some tetra-alkyl ammonium salts, alkyl isonitriles, trimethyl vinyl ammonium salts,[8] pyrrole[9] and the pyridinium ion [10] in which due to the high symmetry of the electrical gradient at the ^{14}N nucleus, quadrupolar relaxation is long enough to allow ^{14}N–^1H coupling to occur. The magnitude of the coupling constant between ^{14}N and directly bonded hydrogen depends on the hybridisation of the nitrogen and is enhanced with increasing *s* character of the bond. By comparing the value of 51.2 Hz obtained in this study for J_{NH} of the protonated nitrogen in benzotriazole ring of acylglycine compounds **1–3** with the reported values for the similar coupling in pyridinium ion ($J_{NH} = 68 \pm 1$ Hz) with sp^2 nitrogen, ammonium ion ($J_{NH} = 54 \pm 0.5$ Hz) and ammonia ($J_{NH} = 46 \pm 2$ Hz) both with sp^3 nitrogen, it is reasonable to assume that protonated nitrogen in benzotriazole is nearly sp^3 hybridised.[11]

Investigation of the cationic properties of analogues of benzotriazole derivatives by ^1H NMR spectroscopy is in progress.

Experimental

Melting points were determined on a Reichert hot plate apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian Unity Plus 400 spectrometer (399.866 MHz for ^1H NMR and 100.556 MHz for ^{13}C NMR) using [$^2H_6$] DMSO as solvent. Chemical shifts (δ) are reported in p.p.m. related to tetramethyl silane (TMS) as internal



Scheme 1

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* To receive any correspondence.

† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

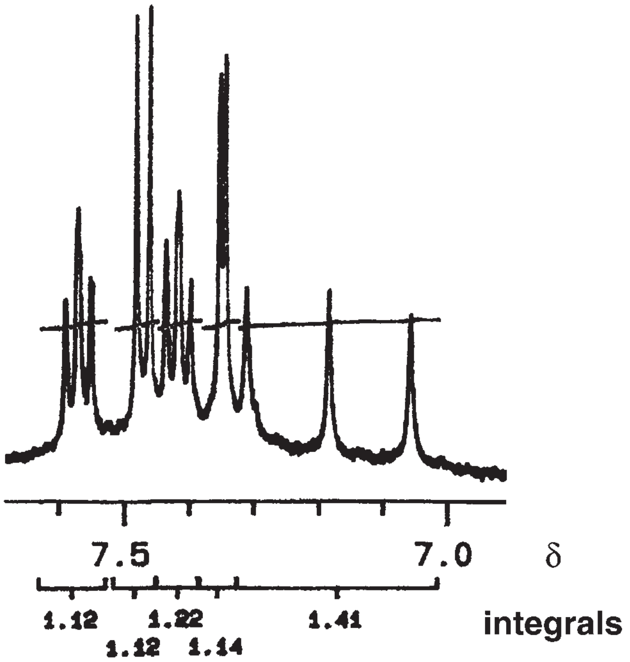

Fig. 1 ^{1}H NMR spectrum of compound **2**.

standard. Mass spectra were obtained on a Finnigan TSQ-70 instrument. IR spectra were recorded on a Nicolet Magna IR 550 spectrometer. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyser.

General procedure for the preparation of α-(benzotriazol-1-yl)-N-acylglycines **1–3**: Benzotriazole (2.38 g, 20 mmol), glyoxylic acid monohydrate (1.84 g, 20 mmol) and the appropriate aromatic amide (20 mmol) in toluene (100 ml) were boiled under reflux in a Dean-Stark apparatus for 3 hours. Compound **1** which was precipitated upon cooling the mixture was purified by washing with ether, recrystallisation from methanol/ether, and drying under high vacuum. For isolation of compounds **2** and **3** the reaction mixture was cooled to room temperature, the solvent was decanted and the residue was triturated with 5 ml of methanol. The resulting precipitate was purified by recrystallisation from methanol/ether.

Preparation of (1-benzotriazol-1-yl)-N-(2-thienylcarbonyl)glycine ethyl ester **4**: A mixture of ethyl glyoxylate (4.2 g, 35 mmol), benzotriazole (2.38 g, 20 mmol), thiophen- 2-carboxamide (2.54 g, 20 mmol) and *p*-toluenesulfonic acid monohydrate (0.1 g) in toluene (100 ml) was boiled under reflux in a Dean-Stark apparatus for 2 hours. After evaporation of the solvent under reduced pressure, the residual oil was triturated with ether and the resulting solid was recrystallised from methanol/ether, washed with ether and dried under high vacuum to give the pure compound **4**.

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Table 1 Physical and spectral data of compounds **1–4**

Entry	mp /°C	Yield /%	^{1}H NMR (δ,ppm)	^{13}C NMR (δ, ppm)	IR(υ/cm^{-1})	Mass *m/z*(M$^+$)	Elemental analyses found calculated/%		
1	205–207	88	7.20(t,1H,J=4Hz,H-4),7.24(t,1H,J_{NH}=51.2Hz),7.44 (t,1H,J=7.6Hz, ArH), 7.56(d,1H, J=4Hz,H-3), 7.60 (t,1H,J=7.6Hz,ArH), 7.87(d, 1H,J=8Hz, CH), 8.05 (d,1H,J=7.6 Hz,ArH), 8.07 (d,1H,J=4Hz,H-5), 8.09 (d,1H,J=7.6Hz, ArH), 10.31 (d,1H,J=8Hz,CONH).	63.7(CH),111.5,119.2,124.2, 127.7, 128.3,130.2,132.2, 132.7,137.6,145.1, 161.4(COOH), 166.9(CONH).	1156,1402, 1549,1622, 1759,3218.	302	C 51.32 (51.65)	H 3. 07 (3.33)	N 18.71 (18.53)
2	185–187	81	6.65 (dd,1H,J=1.6Hz, J=0.8Hz,H-4), 7.19(t,1H, J_{NH}=51.2 Hz), 7.35 (dd,1H, J=1.6Hz, J=0.4Hz, H-3), 7.42(t,1H,J=7.6Hz,ArH),7.47(d,1H, J=8Hz,CH), 7.57 (t,1H,J=7.6Hz, ArH), 7.90 (dd,1H,J=0.8Hz,J=0.4Hz, H-5), 8.05 (d, 1H, J=7.6Hz, ArH), 8.07 (d,1H, J=7.6Hz, ArH), 10.08 (d,1H, J=8Hz,CONH).	63.4(CH),111.7,112.4,116.0,119.3, 124.4,127.9,132.3,145.2, 146.2,146.5, 158.0(COOH),166.9(CONH).	1406,1655, 1733,3144.	286	C 54.41 (54.55)	H 3.30 (3.52)	N 19.79 (19.57)
3	195–196	73	7.07(t,1H,J=4Hz,H-4),7.27(t,1H, J_{NH}=51.2 Hz), 7.37(t,1H,J=7.6Hz, ArH),7.41(d,1H,J=8Hz,CH), 7.49(t,1H, J=7.6Hz, ArH),7.62(d,1H, J=4Hz,H-3), 7.80 (br,1H,H-1),7.96(d,1H,J=4Hz,H-5), 8.00(d, 1H , J=7.6Hz,ArH),8.02(d,1H,J=7.6Hz,ArH),10.02 (d,1H,J=8Hz,CONH).	63.5(CH),111.2,118.9,123.8,127.3, 127.7,130.1,131.7,132.1,137.5,145.1, 161.4(COOH),166.6(CONH).	1408,1659, 1749,3176.	285	C 54.98 (54.74)	H 3.93 (3.64)	N 24.37 (24.55)
4	156–157	87	1.19(t,3H,J=7.2Hz,CH_3),4.26(m,2H,CH_2),7.20(t,1H,J=4Hz,H-4),7.45 (t,1H,J=7.6Hz, ArH), 7.61 (t,1H, J=7.6Hz, ArH), 7.64 (d,1H, J=8Hz, CH), 7.87 (d,1H,J=8Hz,H-3), 8.01(d,1H,J=4Hz,H-5), 8.05 (d,1H, J=7.6Hz,ArH), 8.09 (d,1H, J=7.6Hz, ArH), 10.31(d,1H,J=8Hz,CONH).	13.8(CH_3), 62.5(CH_2), 63.4(CH) , 111.13, 119.2,124.3, 127.8,128.2, 130.2, 132.2, 132.7, 137.3, 145.1,161.3 (COOH), 165.5(CONH).	1156,1276, 1549,1654, 1754,3228.	330	C 54.68 (54.53)	H 4.01 (4.27)	N 16.64 (16.96)