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^{1}HNMR OF PYRAZOLES : EFFECT OF INTERACTION OF CARBAMOYL GROUP WITH ADJACENT CENTERS ON THE CHEMICAL SHIFTS OF CONCERNED PROTONS.

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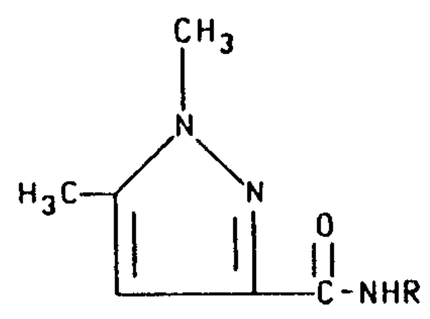
ABSTRACT

The ^{1}HNMR of a series of constitutional isomers of dimethylpyrazole carboxamides revealed the contribution of π and/or n-electrons in deshielding protons α- to CONHR group. Intermolecular hydrogen bonding with polar solvent molecules was able to affect more strongly the CONHR proton chemical shift than intramolecular. The observed pattern of δ values shown by CONHR proton in the derivative R = C_6H_{11} allowed to assign for it a trans axial conformation. Finally a regression equation was derived to draw a linear relation between the chemical shifts of CONHR protons in both isomers.

INTRODUCTION

Different biological activities have been assigned for pyrazoles carrying N-substituted carbamoyl moiety. This is associated not only with analgesic, antiinflammatory and antipyretic group[1] but with other medicines, fungicides and herbicides as well[2-9].

In a previous publication we have reported the synthesis and preliminary biological and metal binding potentialities revealed by constitutional isomers of dimethyl-N-substituted pyrazole carboxamides 1 and 2[10], Scheme 1.



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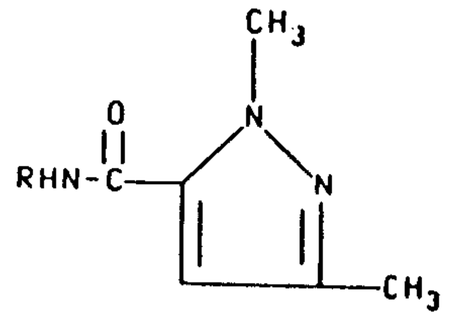

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a, R = H, b, R = CH_3, C, R = C_2H_5, d, R = C_6H_{11} e, R = C_6H_5, f, R = $CH_2C_6H_5$, g, R = NH $CSNH_2$, h, R = NH_2

Scheme 1

In this report ^{1}HNMR of C_4-H, N-CH_3, $C_{3/5}$-CH_3 and CONHR protons of isomers 1 and 2 will be discussed. Deshielding due to intramolecular hydrogen bond, as expected, is restricted to interaction between CONHR proton and pyridinic nitrogen in isomer 1. This report discusses the effect of CONHR group on adjacent centers and gives an equation for the relation between the chemical shifts of CONHR protons in 1 and 2. Moreover, observed solvent shift and anisotropic effect of σ-electrons have been rationalized.

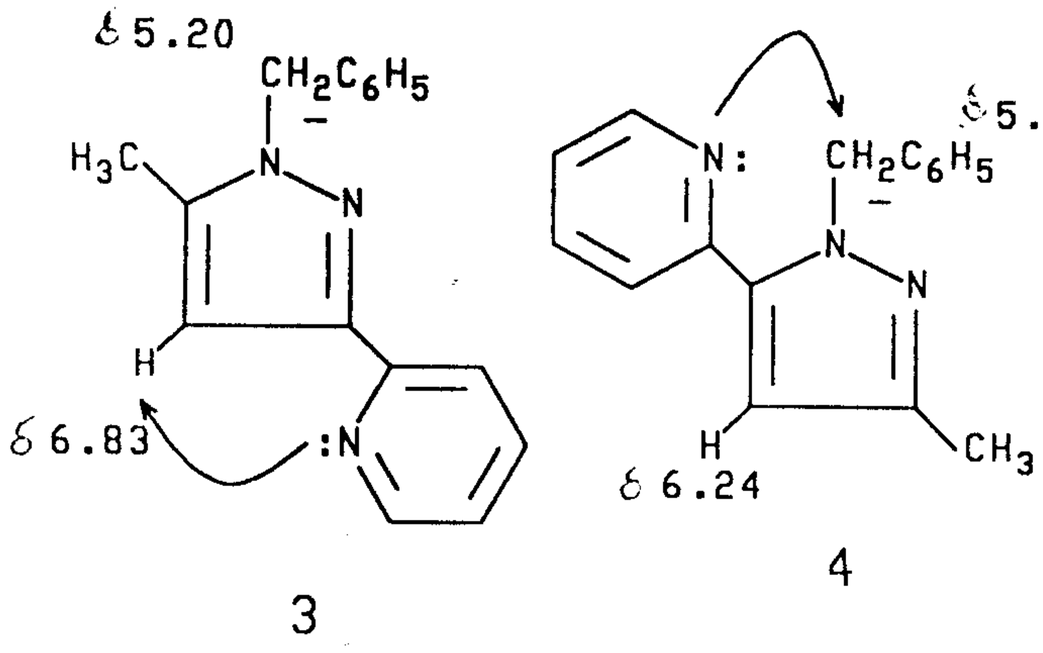
EXPERIMENTAL

^{1}HNMR spectra, table 1, were determined on EM-390,90 MHz instrument with TMS as internal standard.

All spectra were carried out in DMSO-d_6 and in $CDCl_3$ with exception of the derivatives a,f-h which are insoluble in $CDCl_3$.

RESULTS AND DISCUSSION

Several trials with moderate success have been done to correlate ^{1}HNMR chemical shifts and charge densities of the carbon atom to which the proton is bound. The obtained results depend on methods of calculation adopted[11a]. Deshielding of protons α- to 2-pyridyl group in 1-benzyl-5-methyl-3-(2-pyridyl)pyrazole 3, and 1-benzyl-3-methyl-5-(2-pyridyl) pyrazole 4 has been reported. Either C_4-H or benzylic proton will suffer a downfield shift (≈ 0.6 ppm) when α- to the 2-pyridyl group[11a], Scheme 2.



Scheme 2

In our work on using $CDCl_3$ the protons α- to CONHR were considerably deshielded. Thus C_4-H proton in (b-e) is shifted downfield by an average value of 0.5 ppm relative to C_4-H proton in 1,5-dimethylpyrazole. On the other hand in 2 (b-e), protons on α- and $\tilde{\alpha}$- positions relative to CONHR were affected. This may indicate a simultaneous contribution of π-and n-electron clouds of the hetero atoms of CONHR group. Thus N-CH_3 and C_4-H protons were shifted downfield by an average values 0.3 and 0.4 ppm respectively when matched with the corresponding protons in 1,3 dimethylpyrazole, table 2. In both isomers the chemical shift of -CH_3 in ß- position was not affected, and reserved values practically equal to those of the dimethylpyrazoles[11b].

Because of its significance in metal binding, the concerted bonding of pyridinic nitrogen and CONHR proton seemed worthy of study. Intramolecular hydrogen bonding between the two centers looks a plausible probe. It reflects spatial complementarity between the donor and acceptor centers. Actually where intramolecular hydrogen bond was allowed by 1 (b-e), a considerable downfield chemical shift of CONHR protons relative to their analogues of 2(b-e) was observed, table 1. The differences between chemical shifts shown by derivatives (b-e) in isomers 1 and 2 go in parallel with bulkiness of R: where R = CH_3, δ=0.2; R=C_2H_5, δ=0.5; R=c-hexyl, δ=0.66; R=C_6H_5, δ=0.82 ppm.

In DMSO-d_6 the chemical shifts of different protons were differently affected relative to their values in $CDCl_3$. However, prominent downfield chemical shifts were shown by CONHR protons in DMSO-d_6, table 1, this may be attributed to strong dipole-dipole interaction of the type solvent CONHR. The difference between δ values in DMSO-d_6 and $CDCl_3$ ranges from 0.57 to 1.27 ppm for 1 (b-e) and from 1.47 to 2.35 ppm for 2 (b-e). Examination of δ values in DMSO-d_6, shows that CONHR protons in 1(a-h) are clearly shielded relative to those in 2 (a-h). This observation seems opposite to that noticed in $CDCl_3$. However, intervention of intramolecular hydrogen bonding allowed by 1 might be an effective contributing factor in each case. Further more, such contribution might be of lower magnitude relative to intermolecular,

molecule-DMSO-d_6, interaction leading to an orderly reduced δ values of 1 (a-h).

Solvent shifts were reported by Elguero et al[12] on studying ^{1}HNMR of 1-methyl and 1-phenyl substituted pyrazoles. A week upfield shift was noticed for C_3-H and a significant downfield shift was observed for proton C_5-H in DMSO-d_6 compared to $CDCl_3$. This indicated different sensitivity of protons to solvent shift.

Consistency of 2 (a-h) to show higher δ values of CONHR proton in DMSO-d_6 relative to 1 (a-h) analogues led us to search an equation that can describe this proportionality.

The linear regression equation 1 was deduced:

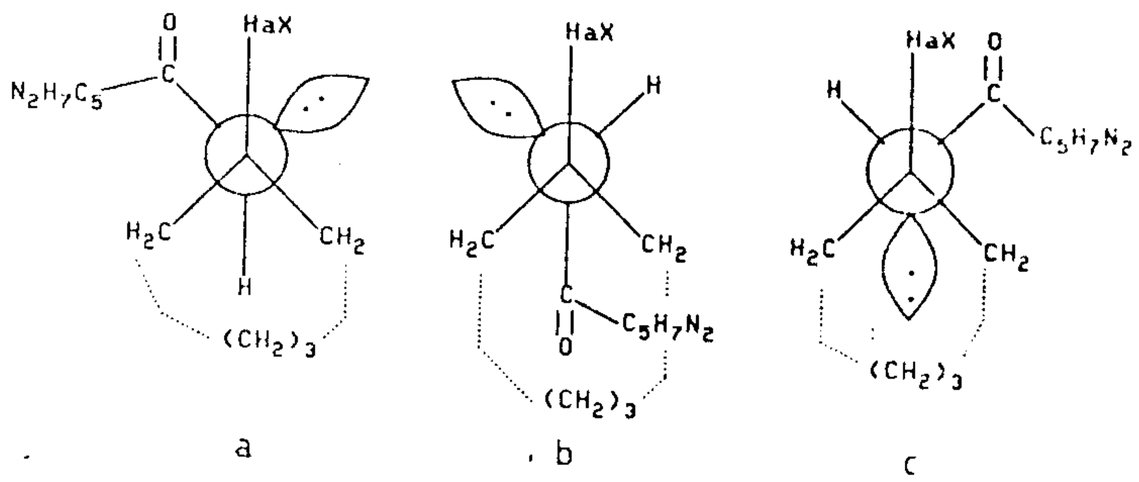
δ^2 (CONHR) = 0.9601 + 0.9329 (± 0.0432) δ^1 (CONHR)

n=8 ; r= 0.9936 ; s= ± 0.12

F=21.62 at P < 0.0001

In equation 1 δ^1 and δ^2 represent the chemical shifts of CONHR protons pertaining to 1 and 2 isomers respectively, n is the number of derivatives (a-h), s is the standard deviation, r is the regression coefficient, F is the confidence limit at the given p value. The regression constant can be regarded as a correction factor counting for included intramolecular hydrogen bonding effect in δ^1 values.

The predicted values from equation 1 are listed in table 3 , where derivative d shows the most deviating δ value. In table 1, the CONHR-C_6H_{11} proton is relatively shielded showing lowest δ values within b-h series in either $CDCl_3$ or DMSO-d_6. Since CONHR-C_6H_{11} bond is mainly equatorial, then NH proton should be axially directed to fall in the shielded zone of C-C bonds of c-hexane ring. Demonstration of such a shielding effect is probably a strong evidence for the persistance of the molecules in trans axial conformation a.



a b c

Therefore in compound d anisotropic effect of σ-electrons of C-C bond should be added to the parameters already discussed affecting CONHR chemical shift. Consequently after exclusion of d from the regression treatment of δ values equation 2, was obtained with lower s values, table 3.

δ^2 (CONHR) = 0.6118 + 0.9701 (±0.0294) δ^1 (CONHR)

n=7, r=0.9977 s=±0.07 F=1088 P < 0.00001

Validity of equation 2 seems to be limited by inter and intramolecular forces affecting CONHR chemical shifts. In a case where liable intervention by other forces, equation 2 will give considerably deviating values.

Table 1: Protons chemical shifts of 1 and 2 (a-h) derivatives in different solvents.

Compound	CDCl$_3$ [*]				DMSO-d$_6$			
	1-CH$_3$	C$_3$/C$_5$ CH$_3$	4-H	5-CONHR	1-CH$_3$	C$_3$/C$_5$ CH$_3$	4-H	5-CONHR
1a					3.73	2.27	6.33	7.10
1b	3.77	2.27	6.57	6.93	3.70	2.23	6.30	7.83
1c	3.80	2.30	6.60	6.83	3.70	2.23	6.30	7.83
1d	3.70	2.23	6.40	6.53	3.75	2.27	6.30	7.40
1e	3.80	2.30	6.57	8.50	3.77	2.27	6.47	9.77
1f					3.77	2.27	6.47	8.53
1g					3.73	2.27	6.47	9.78
1h					3.78	2.30	6.47	9.13
2a					3.96	2.16	6.53	7.50
2b	4.10	2.23	6.37	6.73	3.97	2.20	6.50	8.20
2c	4.10	2.23	6.33	6.33	3.97	2.20	6.51	8.25
2d	4.13	2.27	6.30	5.87	3.97	2.22	6.58	8.07
2e	4.17	2.33	6.50	7.68	3.97	2.20	6.75	10.03
2f					3.93	2.13	6.57	8.78
2g					3.87	2.10	6.57	10.13
2h					3.90	2.10	6.43	9.57

(*) Data is absent for insoluble compounds.

Table 2: Deshielding of protons ortho to CONHR in 1 and isomers.

Compound	solvent	δ(ppm)			
		N-CH$_3$	C$_3$-CH$_3$	C$_5$-CH$_3$	C$_4$-H
1(b-e)	CDCl$_3$	3.70-3.80	----	2.23-2.30	6.4-6.6
1,5-DMP[*]	CDCl$_3$	3.73	----	2.22	5.98[1b]
2(b-e)	CDCl$_3$	4.10-4.17	2.23-2.33	----	6.3-6.5
1,3-DMP[*]	CDCl$_3$	3.80	2.23	----	5.95[11 b]

(*) DMP = dimethylpyrazole.

Table 3 : Predicted chemical shifts of CONHR proton in isomer 2.

Compound	δ^2(CONHR) (ppm)				
	Found	Calcd.[1]	Δ^2	Calcd.[3]	Δ^2
2a	7.50	7.58	-0.08	7.5	0.00
2b	8.20	8.26	-0.06	8.21	-0.01
2c	8.25	8.26	-0.01	8.21	0.04
2d	8.07	7.86	0.21	———	
2e	10.03	10.07	-0.04	10.09	-0.06
2f	8.78	8.92	-0.14	8.89	-0.11
2g	10.13	10.08	0.05	10.10	0.03
2h	9.57	9.48	0.09	9.47	0.10

1) from eq.1; 2) difference between found and calculated values; 3) from eq.2

REFERENCES

1-G.Vertuani, P.Giori, M.Guarneri, and G.P.Sarto, J. Pharm. Sci., 74, 1013 (1985).

2-C.Zenaida, and B.Cornelia, Rev. Med. (Trigu-Mures), 17, 415 (1972); through Chem. Abstr., 76, 153661k (1972).

3-J.G.Buchanon, A.Stobie, and R.H.Wightman, J. Chem. Soc., Perkin Trans. 1, 2374 (1981).

4-H.M.Faid-Allah, and R.Soliman, Pharmazie, 35, 799 (1980).

5-H.M.Mokhtar, and H.M.Faid-Allah, ibid., 42, 481 (1987).

6-M.T.Garcia-Lopez, R.Herranz, and G.Alonso, J. Med. Chem., 22, 807 (1979).

7-M.T.Garcia-Lopez, M.J.Dominguez, R.Heranz, M.Sanchezperez, A. Contreras, and G.Alonso, ibid., 23, 625 (1980).

8-J.L.Huppatz, J.N.Phillips, and B.Witrzens, Agric. Biol. Chem., 48, 45 (1984).

9-J.R.Back, J. Aikins, M.P.lynch, J.R.Rizzo, and E.V.P.Tao, J. Heterocyclic Chem. 26, 3 (1989).

10-T.A.Fadl. A.F.Youssef, A.N.Ahmed and H.I.El-Bitar, Bulletin of Pharmaceutical Seiences Assiut University 13 (2) 145 (1990).

11-J.Elguero, in "Comprehensive Heterocyclic Chemistry", Vol 5, A. Katritzky, and C.W.Ress, Eds., Pergamon Press, Oxford, (1984), [a] 183, [b] 197.

12-J.Elguero, R.Jacquier, and S.Mignonac-Mondon, Bull. Soc., Chim. France, 4436 (1970).

الرنين النووى المغناطيسى للبيرازولات : تأثير تفاعل مجموعة الكاربامويل مع المراكز المجاورة على الازاحة الكيميائية للبروتونات المعنية

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تم دراسة الرنين النووى المغناطيسى لمجموعة مشتقات المتشابهات الوصفية لثنائى ميثيل البيرازول كاربوكساميد والتى اثبتت دور الالكترونات (π, n) فى عدم حجب البروتونات الموجودة فى وضع الفا بالنسبة لمجموعة الكاربامويل. وقد لوحظ التأثر الشديد لبروتون الكاربامويل بواسطة المذيب القطبى.

وبملاحظة نمط O للبروتون حيث $R = C_6 H_{11}$ قد امكن اقتراح الوضع ترانس محورى لهذا المركب. ولقد تم استنباط معادلة خطية تبين العلاقة بين مقدار تغير قيمة δ للبروتونات الاميدية فى أى الموضعين ٣ ، ٥ بمعلومية احدهما.

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