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Protonation effect on chemical shifts of some piperidones — unusual influence by anions

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^{1}H and ^{13}C NMR spectra are recorded for twelve picrate derivatives **4-15** derived from some 3-alkyl-2,6-diarylpiperidin-4-ones and 3,5-dimethyl-2,6-diarylpiperidin-4-ones. The difference in the chemical shift of equatorial methylene proton and axial methylene proton at C(5) [$\Delta = \delta_{eq} - \delta_{ax}$] is highly negative in **4-13** which is in contrast to the value observed in the corresponding parent piperidin-4-ones and this is attributed to the *syn* 1,3-diaxial interaction between the axial N-H bond and axial hydrogen at C-5. The effect of protonation on the chemical shifts was studied in detail. The chemical shifts of the heterocyclic ring protons are influenced by the picrate anion.

Keywords: NMR data, picrates, anion influence

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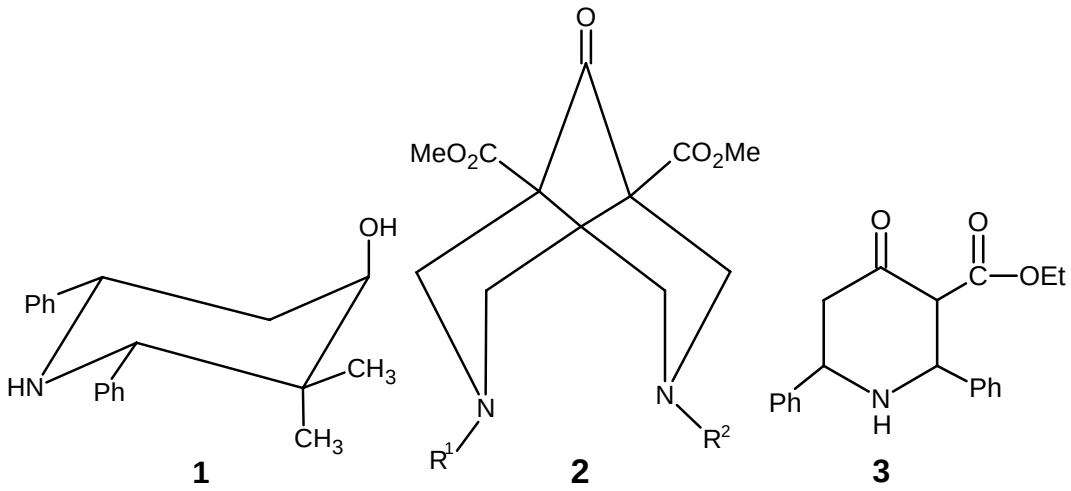
The relative chemical shift order of equatorial and axial protons in the normal chair conformation of cyclohexane and its derivatives ($\delta_{eq} > \delta_{ax}$) is attributed to the magnetic anisotropic effect of the C-C single bonds. The influence of substituents on the chemical shifts of protons attached to the adjacent carbon has been studied in detail[1-3]. In normal chair conformation, it has been reported[4] that the equatorial substituent at β- or γ-position cannot affect the $\delta_{eq} - \delta_{ax}$ significantly. However, a γ-axial substituent or β-axial substituent can decrease $\delta_{eq} - \delta_{ax}$ value significantly. The negative value[4] is even reported in *t*(4)-hydroxy-3,3-dimethyl-r(2),*c*(6)-diphenylpiperidine **1** where axial hydrogen at C-5 experiences severe 1,3-diaxial interaction with axial methyl group at the γ-position [C(3)] and deshielding magnetic anisotropic effect of axial hydroxy group at the β-position [C(4)].

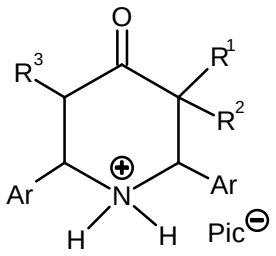
Gogell *et al.*[5] have reported an unexpected deviation from the axial/equatorial chemical shift order ($\delta_{ax} > \delta_{eq}$) in the 1,5-dicarboxymethylbispidinones **2**. The carboxymethyl group increases the chemical shifts of the axial protons more than that of equatorial protons especially with a keto group in the β-position. Similar enhancement of chemical shift of axial proton has also been noted[6] in some *t*(3)-carboxyethyl-r(2),*c*(6)-diphenylpiperidine derivatives **3**. We thought that protonation of piperidine nitrogen may change $\delta_{eq} - \delta_{ax}$ value significantly. Since there is no systematic study regarding the effect of protonation on the chemical shifts, we decided to investigate the effect of protonation on the chemical shifts of methylene protons in some piperidine derivatives. Crystal studies of *N*-aminobenzimidazolium picrate[7] and 3-amino-1-methyl-4,5′-dihydropyrazol-2-ium picrate[8] were reported in literature. This prompted us to prepare the picrates of some 3-alkyl-2,6-diarylpiperidines to study the effect of protonation on the chemical shifts. In the present study picrates **4-15** were prepared and high resolution NMR spectra were recorded. The $\delta_{eq} - \delta_{ax}$ value for the methylene protons at C-5 (β methylene protons) is highly negative in these cases. To our surprise the chemical shifts of heterocyclic ring protons are influenced by the picrate anion and to our knowledge this is the first report of the influence of the anion on the chemical shifts.

Results and Discussion

Treatment of picric acid with piperidin-4-ones may lead to either molecular addition compounds or the corresponding piperidinium picrates  . The



1 **2** **3**



4-15

	R^1	R^2	R^3	Ar
4;	Me	H	H	C_6H_5
5;	Me	H	H	*p*-$OMeC_6H_4$
6;	Me	H	H	*p*-ClC_6H_4
7;	Me	H	H	C_4H_3O
8;	Et	H	H	C_6H_5
9;	Et	H	H	C_4H_3O
10;	CO_2Et	H	H	C_6H_5
11;	*i*-Pr	H	H	C_6H_5
12;	*i*-Pr	H	H	C_4H_3O
13;	CH_3	CH_3	H	C_6H_5
14;	CH_3	H	CH_3	C_6H_5
15;	CH_3	H	H	C_4H_3O

C_4H_3O = 

Table I — Coupling constants (Hz) of some piperidin-4-one picrates **4-15**

Compd	$J_{2,3}$	$J_{5,6}$	$J_{5a,5e}$	$J_{H\text{-}CH_3}$
4	12.46	13.79 ($J_{6a,5a}$) 3.06 ($J_{6a,5e}$)	14.63	6.61
5	12.48	14.24 ($J_{6a,5a}$) 3.14 ($J_{6a,5e}$)	14.49	6.46
6	12.37	13.93 ($J_{6a,5a}$) 2.61 ($J_{6a,5e}$)	14.72	6.58
7	12.35	13.52 ($J_{6a,5a}$) 3.20 ($J_{6a,5e}$)	15.20	6.61
8	12.45	13.28 ($J_{6a,5a}$) 2.91 ($J_{6a,5e}$)	14.85	7.38
9	–	3.40 ($J_{6a,5e}$)	14.96	7.41
10	11.32	12.30 ($J_{6a,5a}$) 2.92 ($J_{6a,5e}$)	14.17	7.14
11	12.06	12.96 ($J_{6a,5a}$) 3.35 ($J_{6a,5e}$)	15.57	6.82; 6.86
12	11.34	12.38 ($J_{6a,5a}$) 3.56 ($J_{6a,5e}$)	14.97	7.01; 7.13
13	–	–	–	6.61
14	12.47	–	12.47	6.48
15	9.34	9.34 ($J_{6a,5a}$)	–	6.54

formation of molecular addition compounds is ruled out based on the conductance studies measured in acrylonitrile. The molar conductance values are in the ratio of 1:1 electrolyte thus supporting the formation of piperidinium picrate only. The high resolution ^1H and ^{13}C NMR spectra were recorded for the picrates **4-15.** The signals in the ^1H NMR spectra were assigned based on their positions, integrals and multiplicities. The coupling constants are readily obtained from the spectra using first order analysis for all the compounds except the carbethoxy compound **10**. For **10** analysable ABX spectrum was obtained from which coupling constants were determined using second order analysis. The coupling constants and chemical shifts determined in this manner are displayed in **Tables I** and **II** respectively.

The observation of large (~ 11Hz) and small (~ 4Hz) couplings about C(5)-C(6) bond and one large (~ 10 Hz) coupling about C(2)-C(3) bond in **4-12** (**Table I**) confirms equatorial orientation of alkyl

Table II —^{1}H Chemical shifts (ppm) of picrates **4-15** and their parent piperidin-4-ones

Compd	H(2)	H(3)	H(5)	H(6)	Pic^-	Alkyl	Aromatic
4	4.22 (3.63)	3.58 –	3.78 (ax); 2.82 (eq) [2.74 (ax); 2.83(eq)]	4.63 (4.10)	8.97	0.92 (CH_3) [0.84 (CH_3)]	7.49-7.42; 7.36-7.26 [7.48-7.44; 7.39-7.24]
5	4.10 (3.56)	3.58 –	3.85 – 3.71 (ax); 2.79 (eq) [2.55-2.81(ax) & (eq)]	4.52 (4.02)	8.85	3.75 (OCH_3); 0.94 (CH_3) [3.81, 3.79 (OCH_3); 0.82 (CH_3)]	7.47-7.36; 6.81-6.72 [7.22-7.01; 6.86-6.76]
6	4.37 (3.60)	3.57 (2.56 – 2.69)	3.75 (ax); 2.81 (eq) [2.56 – 2.69 (ax) & (eq)]	4.77 (4.06)	8.93	0.92 (CH_3) [0.82 (CH_3)]	7.53-7.46; 7.32-7.28 [7.41-7.38; 7.35-7.31]
7	4.55 (3.80)	3.40 (2.88 – 2.81)	3.52 (ax); 2.75 (eq) [2.81-2.88 (ax); 2.72 (eq)]	4.90 (4.17)	8.72	0.89 (CH_3) [0.92 (CH_3)]	7.36-7.35; 6.54-6.52; 6.33-6.32 [7.39-7.35; 6.34-6.29, 6.22]
8	4.70 (3.72)	3.20 –	3.35 (ax); 2.76 (eq) [2.73 (ax); 2.61 (eq)]	4.95 (4.07)	8.62	1.34 (CH_2CH_3); 0.76 (CH_2CH_3) [1.58 (CH_2CH_3); 1.17 (CH_2CH_3)]	7.62-7.58; 7.53-7.47 [7.49-7.43; 7.39-7.24]
9	4.59 (3.92)	3.17 (2.75 – 2.69)	3.38 (ax); 2.73 (eq) [2.84 (ax); 2.75 – 2.69 (eq)]	4.84 (4.16)	8.70	1.46, 1.32 (CH_2CH_3); 0.75 (CH_2CH_3) [1.59, 1.28 (CH_2CH_3); 0.80 (CH_2CH_3)]	7.41-7.39; 6.49-6.47, 6.35 [7.39-7.36; 6.34-6.29; 6.22-6.21]
10	4.56 (4.41)	4.00 (3.68)	3.03 (ax); 2.76 (eq) [2.68 (ax); 2.68 (eq)]	4.32 (4.18)	9.10	4.07 ($CO_2CH_2CH_3$; 1.10 (CH_3) [4.06, 4.08 ($CO_2CH_2CH_3$); 1.09 (CH_3)]	7.52-7.43; 7.38-7.26 [7.54-7.27]
11	4.60 (3.99)	2.75 –	3.75 (ax); 3.59 (eq) [2.67 (ax); 2.55 (eq)]	4.76 (4.09)	8.95	1.73 [$CH(CH_3)_2$]0.83; 1.10 (CH_3) [1.66 ($CH(CH_3)_2$); 1.02, 0.88 (CH_3)]	7.53, 7.35, 7.33 [7.50-7.47; 7.43-7.22]
12	4.60 (4.19)	3.25 (2.85)	3.36 (ax); 2.91 (eq) [2.79 (ax); 2.71 (eq)]	4.65 (4.22)	9.11	2.07 [$CH(CH_3)_2$]; 1.10, 0.81 (CH_3) [1.97 [$CH(CH_3)_2$]; 1.05, 0.79 (CH_3)]	7.38-7.26; 6.33-6.22 [7.41-7.29; 6.36-6.23]
13	3.68-3.63 (3.82)	–	2.94-2.79 (ax); 2.94 – 2.79 (eq) [2.93 (ax); 2.48 (eq)]	3.68 - 3.63 (4.06)	8.88	0.86, 0.83 (CH_3) –	7.51-7.43; 7.38-7.24 [7.52-7.44; 7.40-7.26]
14	4.27 (3.62)	3.63 (2.80)	3.63 (2.80)	4.27 (3.62)	9.00	0.93 (CH_3) [0.84 (CH_3)]	7.53-7.50; 7.34-7.31 [7.47-7.44; 7.41-7.25]
15	4.77 (3.75)	3.31 (2.94)	3.31 (2.94)	4.77 (3.75)	8.60	0.86 (CH_3) [0.91 (CH_3)]	6.71-6.70; 6.59-6.57 [7.38, 6.32, 6.27]
16	4.35	3.93	4.17 (ax); 2.74 (eq)	4.59	–	1.43 (CH_2CH_3); 0.82 (CH_2CH_3)	–

Values in the parentheses are the corresponding piperidin-4-ones.

groups at C(3) and aryl groups at C(2) and C(6). The observation of large coupling about C(2)-C(3)/C(5)-C(6) bond in 3,5-dimethyl compounds **14** and **15** confirms the equatorial orientations of alkyl and aryl groups at C(3)/C(5) and C(2)/C(6) respectively. Hence, all the compounds **4-15** exist in normal chair conformation with equatorial orientations of all the substituents similar to their corresponding parent piperidin-4-ones.

In compounds **4-12** the coupling constants about C(2)-C(3) bond are considerably lower than the *trans* couplings about C(5)-C(6) bond. The alkyl groups at C-3 experience severe *gauche* interaction with the aryl groups at C-2 and in order to avoid this *gauche* interaction the ring is flattered about C(2)-C(3) bond. This flattering is responsible for the lower magnitude of $J_{2a,3a}$ relative to $J_{6a,5a}$. Increasing bulkiness of substituent at C-3 decreases $J_{2,3}$ to a greater extent.

It is seen from **Table II** that the chemical shifts of H(2) are considerably lower than that of H(6) in compounds **4-9, 11** and **12**. This also supports the equatorial orientation of alkyl groups at C-3 in **4-9**, **11** and **12**. The magnetic anisotropic effect of C-alkyl bond is responsible for the lower magnitude of H(2) compared with H(6) in these compounds. Similar upfield shift has been reported on the nearby axial proton by the introduction of equatorial substituent by Booth[9].

It is interesting to note that the chemical shifts of H_{5a} (β-methylene proton) are considerably higher when compared to H_{5e} in **4-12** *i.e.*, $\delta_{eq} - \delta_{ax}$ is negative in these cases. In the protonated piperidine derivatives the axial N-H bond experiences severe *syn* 1,3-diaxial interaction with axial hydrogens at C(5) [H_{5a}] and C(3) [H_{3a}] and due to these interactions the protons are deshielded to a greater extent and the corresponding carbons are shielded (**Figure 1**).

Booth and Little[3] have recorded NMR spectra of some *N*-alkyl piperidines in CCl_4 as well as in CF_3COOH [protonation occurs in strongly acidic medium] and observed considerable deshielding on

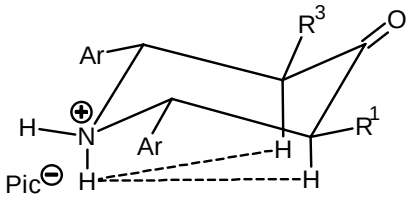
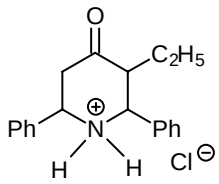


Figure 1



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both the axial and equatorial methylene protons at C(2) and C(6) (α methylene protons) due to protonation. Deshielding magnitude observed on these protons may be due to the change in the electronegativity of nitrogen and the magnetic anisotropic effect of the additional axial N-H bond present in the protonated derivatives. The order of the chemical shifts of the methylene protons at C(2) and C(6) (α-methylene protons) is not reversed (δ_{eq}->δ_{ax}) in the protonated derivatives. This study clearly reveals that *syn* 1,3-diaxial interaction only changes the order of chemical shifts of methylene protons (δ_{ax} > δ_{eq}) rather than the magnetic anisotropic effect.

In order to determine the effect of protonation on chemical shifts, the chemical shifts of picrates **4-15** were compared with the parent piperidin-4-ones[6,10-12]. **Table II** reveals that picrate formation deshields H(2) and H(6) to a greater extent. In the protonated piperidine derivatives the two protons at nitrogen occupy axial and equatorial orientations. The magnetic anisotropic effect of the axial N-H bond is responsible for the greater downfield shift observed on H(6) and H(2) in **4-15**.

It is also seen that H(3) and H_{5a} are deshielded to a greater extent. However, slight variations are observed in H_{5e}. This can be explained by *syn* 1,3-diaxial interaction as shown in **Figure 1**. Picrate formation deshields the alkyl protons at C-3 also. In order to find out whether the chemical shifts are influenced by the anion picrate, the ^{1}H chemical shifts of 3-ethyl piperidinium chloride **16** (ref. 13, **Table II**) have been compared with 3-ethyl piperidinium picrate **8**. The chemical shifts of H(2) and H(6) are considerably higher (that too roughly same magnitude ≈ +0.35 ppm) in 3-ethyl piperidinium picrate **8**. However, the axial protons at C-3 [H(3)] and C-5 [(H_{5a})] in the picrate derivative resonate considerably at upfield [≈ -0.8 ppm] compared to the 3-ethyl piperidinium chloride. This clearly reveals that the anion also significantly influences the chemical shift of heterocyclic ring protons in the cationic moiety. Probably, the π-π interaction between the picrate ring and >C=O group and aryl rings at C(2) and C(6) is responsible for the observed differences in the chemical shifts of the 3-ethyl piperidinium picrate **8** and 3-ethyl piperidinium chloride **16**. Thus, the anion picrate significantly influences the chemical shift. Moreover, comparison of chemical shifts of ring protons in picric acid (9.34 ppm) with those of the picrate derivatives **4-15** also reveals considerable shielding due to picrate formation. This also supports that π-π interaction may be responsible for the variation of the chemical shifts of ring protons in the cationic moiety and anionic moiety in the picrate derivatives.

All these observations confirm that the anion also influences the chemical shifts significantly. Talanavo *et al.*[14] have compared the ^{1}H NMR spectral data of the alkali metal picrate complexes of aromatic group containing crown ethers with those of alkali metal picrate complexes of crown ethers without the aromatic ring. The $\delta_{H\text{-}Pic}$ of the alkali metal picrate complexes of crown ethers with benzo group are considerably lower than the corresponding complexes without benzo group. Shielding of the picrate protons is attributed to Pic–CE–π–π interaction by them.

The ^{13}C NMR spectra have been recorded for **4-15** and the values are displayed in **Table III**. The aromatic carbons could be readily distinguished by their characteristic absorption above 100 ppm. Assignments for the heterocyclic ring carbons and alkyl carbons have been made on the basis of known effects of alkyl substituents in six-membered ring compounds.

It is seen from **Table III** that protonation shields all carbons. The shielding magnitude observed on C(3) and C(5) carbons is more than that of C(2) and C(6) carbons. Due to protonation the axial N-H bond experiences severe *syn* 1,3-diaxial interaction with axial hydrogens at C(3) and C(5) and due to these interactions the protons H_{3a} and H_{5a} are deshielded and the corresponding carbons C(3) and C(5) are shielded. Similar effect has been observed in *N*-methylpiperidin-4-one on protonation by Hirsch and Havinga[15].

Experimental Section

3-Alkyl and 3,5-dimethyl-2,6-diarylpiperidin-4-ones were prepared as per literature procedure[10,16]. The

Table III —^{13}C Chemical shifts (ppm) of picrates **4-15** and their parent piperidin-4-ones

Compd	C(2)	C(3)	C(4)	C(5)	C(6)	Alkyl
4	66.79 (68.40)	46.09 (51.60)	204.00 (209.50)	43.75 (50.90)	60.78 (61.50)	10.15 (*C*H$_3$) [10.10 (*C*H$_3$)]
5	66.39 (67.70)	46.49 (51.70)	204.15 (209.80)	44.03 (51.00)	60.32 (60.90)	10.36 (O*C*H$_3$) [55.24 (O*C*H$_3$)]
6	65.06 (67.80)	45.57 (51.67)	202.45 –	43.19 (50.81)	59.17 (60.96)	9.75 (*C*H$_3$) [10.04 (*C*H$_3$)]
7	58.14 (60.60)	45.66 (49.50)	202.75 (208.00)	42.16 (46.40)	52.68 (54.00)	10.76 (*C*H$_3$) [10.14 (*C*H$_3$)]
8	63.06 (66.70)	51.68 (58.40)	203.26 (209.10)	44.54 (51.60)	58.93 (61.80)	17.48 (*C*H$_2$CH$_3$); 10.61 (CH$_2$*C*H$_3$) [17.80 (*C*H$_2$CH$_3$); 12.20 (CH$_2$*C*H$_3$)
9	55.96 (58.80)	50.95 (56.20)	201.81 (207.60)	42.01 (47.00)	51.90 (54.00)	17.65 (*C*H$_2$CH$_3$); 10.65 (CH$_2$*C*H$_3$) [18.2 (*C*H$_2$CH$_3$); 11.80 (CH$_2$*C*H$_3$)]
10	61.84 (63.20)	60.28 (65.0)	197.90 (202.90)	43.55 (49.80)	58.81 (60.60)	61.31 (O*C*H$_2$CH$_3$); 13.50 (OCH$_2$*C*H$_3$) [60.7 (O*C*H$_2$CH$_3$); 13.70 (OCH$_2$*C*H$_3$)]
11	68.75 (64.90)	59.67 (61.30)	207.72 (209.00)	49.67 (52.10)	64.76 (61.30)	30.30 (*C*H(CH$_3$)$_2$; 24.85, 21.18 (*C*H$_3$) [26.10 (*C*H(CH$_3$)$_2$; 17.8, 21.1 (*C*H$_3$)]
12	53.99	42.11	201.72	39.51	51.36	25.28 (*C*H(CH$_3$)$_2$); 17.15, 19.19 (*C*H$_3$)
13	68.86 (69.50)	51.84 (49.80)	210.94 (212.70)	47.10 (47.20)	63.00 (61.60)	10.46, 10.16 (*C*H$_3$) [20.40, 19.90 (*C*H$_3$)]
14	66.12 (68.80)	45.44 (52.00)	205.06 (211.10)	45.44 (52.00)	66.12 (68.80)	10.17 (*C*H$_3$) [10.50 (*C*H$_3$)]
15	56.27 (61.10)	44.56 (49.60)	203.44 (209.70)	44.56 (49.60)	56.27 (61.10)	10.38 (*C*H$_3$) [10.50 (*C*H$_3$)]

Values in the parentheses are the corresponding piperidin-4-ones

piperidinium picrates **4-15** were prepared by mixing equimolar solution of piperidin-4-one in ethanol (10 mmole) with picric acid in ethanol (10 mmole) and stirring the solution for 40 min. The yellow needles formed were recrystallised twice in benzene.

NMR measurements

Proton spectra were recorded on a BRUKER AMX-400 NMR instrument operating at 400 MHz. Samples were prepared by dissolving 10 mg of the substance in 0.5 mL of $CDCl_3$ containing 1% TMS. The spectral parameters used are: number of scans, 32; number of data points, 32 K; spectral sweep width 4000 Hz.

Proton decoupled ^{13}C NMR spectra were recorded on a BRUKER AMX-400 NMR instrument operating at 100 MHz. Solutions for the measurement of spectra were prepared by dissolving 0.5g of the sample in 2.5 mL of $CDCl_3$ containing few drops of TMS as internal reference. The solvent chloroform-d_6 also provided the internal field frequency lock signal. The spectral parameters used are: number of scans, 5000; number of data points, 32 K; pulse width, 6μs (45°); spectral sweep width, 22000 Hz.

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