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Effect of solvent change on chemical shifts of 4-benzyl-4-hydroxypiperidines

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4-Benzyl-4-hydroxypiperidines **1-8** have been synthesized through Mannich reaction and were characterized through high resolution ^{1}H and ^{13}C NMR spectra in $CDCl_3$.The conformational studies of the above eight compounds have been thoroughly done by using proton and ^{13}C spectral data and the assigned conformations were also supported by Hybrid HF/DFT B3LYP/6-3G* calculations. These results are published earlier by us. In order to study the effect of solvent on the chemical shifts of these piperidines, ^{1}H NMR spectra were recorded in C_6D_6 and DMSO-d_6. The effect of change of solvents results appreciable change in the chemical shifts of various protons in the title compounds.

Keywords: 4-Benzyl-4-hydroxypiperidines, ^{1}H NMR, ^{13}C NMR, Solvent effect, Chemical shifts

The Mannich reaction is an organic reaction which involves the condensation of aromatic aldehydes, ketones and a base substance like ammonia or ammonium acetate in ethanol medium. Piperidin-4-ones are a family of heterocyclic organic compound derived from the respective aldehydes, ketones and ammonium salt. Piperidines are pharmaceutically active compounds which is a key molecular fragment available in natural and pharmaceutically active compounds. Several methods of the synthesis of tertiary alcohols with good yields and high levels of enantioselectivity have been reported.[1-6] The stereochemistry of several 4-substituted-4-hydroxypiperidines have also been established from NMR measurements [7-10] and using chiral bidendate NMR solvent BMBA-p-Me (bis-1,3-methylbenzylamine-2-methylpropane)[11]. Study of 4,4-disubstituted piperidines is of considerable interest since these compounds have been shown to be pharmacologically active and, therefore, they can be extensively used in the clinical field[12-16]and as monomers in the preparation of photoregiomaterials[17] with high transparency.

Chemical shifts are often sensitive to changes of solvent. If the dissolved substance interacts with the solvent a shift in the positions of the signals is observed. The shielding contribution of the solvent to a proton in a solute molecule is expressed in terms of five separate effects. The terms σB, σW, σA and σE are associated with the effects due to bulk magnetic susceptibilities, van der Waals' interactions, diamagnetic anisotropy of the solvent and electric polarization and polarizability of the solvent, respectively. The term σC arises due to weak interactions such as charge transfer and hydrogen bonding which lead to some form of complex in which the solute and solvent molecules are specifically oriented with respect to each other. Bothner-By and Glick20 have shown that σB is of less importance and hence contribution from this term is negligible, by employing an internal chemical shift reference (TMS). The magnitude of σW for non-polar solutes in any given solvent is reasonably constant (± 0.05 ppm) and this effect is also minimised by using internal reference TMS.

The chemical shifts determined in aromatic solvents correspond to higher shielding relative to that of isolated molecule. The shielding regions of these molecules are more exposed than the deshielding regions which are partially occupied by the ring protons or substituents and hence the solute molecules are shielded. Substantial changes in aromatic solvents occur due to variety of interactions such as electric dipole-dipole, electric dipole-quadruple, charge transfer and hydrogen bond association which result in specific solvent solute orientations. Thus, the diamagnetic anisotropy of the solvent will often make a contribution through the term σC.

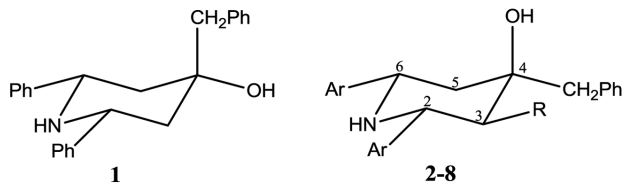
Experimental Details

Synthesis of 4-benzyl-4-hydroxypiperidines 1-8[18]

In moisture free appropriate glassware set up, 0.6 g (0.025 mol) of clean, dry magnesium turnings, 25 mL of sodium metal dried ether and a small crystal of iodine were placed. The separating funnel was charged with a solution of 3 mL (0.025 mol) of freshly distilled benzyl chloride in 25 mL of sodium dried ether. About 12 mL of this solution was allowed into the reaction flask and the flask was partially immersed in a water bath maintained at 40°C. The flask was immediately removed from the bath and the mixture was stirred. The remaining benzyl chloride was added during 30 min and the vigorous reaction was controlled by immersing the flask in ice-water. Then the reaction mixture was refluxed for further 15 min. The flask was cooled again by bath of ice-water. A solution of appropriate piperidin-4-one (0.0125 mol) in sodium dried ether was added to vigorously stirred benzyl magnesium chloride solution at such a rate that the mixture refluxed gently (about 1 h).

The reaction mixture was once again refluxed for 48 h, cooled and poured slowly with constant stirring into a mixture of crushed ice (125 g), 100 mL water and 10-20 mL of concentrated hydrochloric acid contained in a 500 mL beaker. The ether layer was separated by separating funnel and the aqueous layer was extracted with 50 mL ether and the combined ether solutions were washed with water. The hydrochloride thus obtained in ether layer was filtered and dried at the pump. The dried hydrochloride was pasted with 2 or 3 drops of acetone and neutralized with aqueous ammonia followed by the addition of water. The tertiary alcohols obtained were chromatographed and recrystallised from benzene-petroleum ether mixture.

The structures of compounds **1-8** are shown in Fig. 1. The melting points are as follows: 124-125°C (**1**); 112-120°C (**2**); 198-199°C (**3**); 148-149°C (**4**); 168-169°C (**5**); 154-155°C (**6**); 190-191°C (**7**) and 182-183°C (**8**).



	Ar	R
2	Ph	H
3	Ph	CH_3
4	*p*-ClC_6H_4	CH_3
5	*p*-$CH_3OC_6H_4$	CH_3
6	Furyl	CH_3
7	Ph	C_2H_5
8	*p*-ClC_6H_4	C_2H_5

Fig. 1 — Structures of compounds **1-8**

Results and Discussion

Effect of change of solvent from $CDCl_3$ to DMSO-d_6

For the synthesized tertiary alcohols, ^1H and ^{13}C NMR spectra were recorded and the conformations of functional groups have been assigned based on the chemical shift and coupling constant values[19]. In order to study the influence of solvent on the ^1H chemical shifts of 4-benzyl-4-hydroxypiperidines the high resolution ^1H NMR spectra were recorded in C_6D_6 and DMSO-d_6. The chemical shift values are derived from these spectra and the values have been compared with those recorded in $CDCl_3$. Tables 1 and 2 report the comparison of chemical shifts of 4-benzyl-4-hydroxypiperidines obtained in different solvents.

Table 1 reveals that there is no appreciable change in the chemical shifts of H(6) in 3-alkyl-2,6-diphenyl tertiary alcohols **3** and **7** and their *p*-chloro derivatives **4** and **8** due to the variation of solvent from $CDCl_3$ to DMSO-d_6. The chemical shifts of all the other heterocyclic ring protons and alkyl protons at C(3) are shielded in DMSO-d_6 compared to $CDCl_3$. The shielding observed on H(3) and H_{5a} in DMSO-d_6 are considerably greater than those observed on the other ring protons.

The OH group at C(4) and NH group are more solvated in DMSO-d_6 compared to other protons in the 4-benzyl-4-hydroxypiperidines. The upfield shifts observed in 4-benzyl-4-hydroxypiperidines due to the replacement of $CDCl_3$ by DMSO-d_6 are due to specific molecular association involving intermolecular hydrogen bonding between solute and solvent molecules. Due to this hydrogen bonding *syn*-1,3-diaxial interaction between hydroxyl group at C(4) and benzylic protons [H(2) and H(6)] are relieved and hence these protons resonate at lower frequency in DMSO-d_6 compared to that observed in $CDCl_3$. Solvation also decreases *syn*-1,3-diaxial interaction between H(3) and H_{5a} and hence these protons also absorb at lower frequency in DMSO-d_6 compared to $CDCl_3$. In addition the magnetic anisotropic effect of S=O bond of DMSO-d_6 also may contribute to the shielding observed in these systems.

Effect of change of solvent from $CDCl_3$ to C_6D_6

It is inferred from Table 2 that replacement of $CDCl_3$ by magnetically anisotropic solvent C_6D_6 deshields all the heterocyclic ring protons in 4-benzyl-

Table 1 — ^{1}H chemical shifts (ppm) of some 4-benzyl-4-hydroxypiperidines in $CDCl_3$ and DMSO-d_6

Compound	Solvent	H(2)	H(3)	H_{5a}	H_{5e}	H(6)	Alkyl protons	CH_2Ph
4-Benzyl-*c*(4)-hydroxypiperidine1	$CDCl_3$	4.15	Same as H(5)	1.76-1.66	1.92	4.15	-	3.16
	DMSO-d_6	4.07		1.42	1.65	4.07	-	3.03
4-Benzyl-*t*(4)-hydroxypiperidine2	$CDCl_3$	4.19	Same as H(5)	1.76-1.66		4.19		2.79
	DMSO-d_6	4.11		1.38	1.55	4.11	-	2.68
4-Benzyl-*t*(4)-hydroxy-3-methyl-2,6-diphenylpiperidine 3	$CDCl_3$	3.86	1.83	1.75	1.62	4.10	0.86	3.06 2.69
	DMSO-d_6	3.77	1.56	1.50-1.45		4.08	0.72	2.81 2.72
4-Benzyl-*t*(4)-hydroxy-3-methyl-2,6-bis- (*p*-chlorophenyl)piperidine4	$CDCl_3$	3.84	1.75	1.66	1.57	4.08	0.84	3.04 2.68
	DMSO-d_6	3.78		1.54-1.39		4.09	0.69	2.83 2.72
4-Benzyl-*t*(4)-hydroxy-3-methyl-2,6-di-2′-furylpiperidine6	$CDCl_3$	4.02	2.01	1.87	1.71	4.18	0.92	2.73 3.07
	DMSO-d_6	3.85	1.64	1.53	1.59	4.10	0.78	2.78 2.07
4-Benzyl-*t*(4)-hydroxy-3-ethyl-2,6- diphenylpiperidine7	$CDCl_3$	3.92	1.58	1.78	1.63	4.06	1.80, 1.21 (CH_2CH_3) 0.52 (CH_2CH_3)	3.15 2.66
	DMSO-d_6	3.85	1.33	1.49	1.42	4.05	1.73, 1.06 (CH_2CH_3) 0.39 (CH_2CH_3)	2.93 2.68
4-Benzyl-*t*(4)-hydroxy-3-ethyl-2,6-bis- (*p*-chlorophenyl)piperidine8	$CDCl_3$	3.91	1.47	1.64	1.53	4.03	1.75, 1.17 (CH_2CH_3) 0.55 (CH_2CH_3)	2.64 3.13
	DMSO-d_6	3.84	1.28	1.44-1.39		4.03	1.03, 1.73 (CH_2CH_3) 0.41 (CH_2CH_3)	2.92 2.67

Table 2 — ^{1}H chemical shifts (ppm) of some 4-benzyl-4-hydroxypiperidines in $CDCl_3$ and C_6D_6

Compound	Solvent	H(2)	H(3)	H_{5a}	H_{5e}	H(6)	Alkyl protons	CH_2Ph
4-Benzyl-*c*(4)-hydroxypiperidine1	$CDCl_3$	4.15	Same as H(5)	1.76-1.66	1.92	4.15	-	3.16
	C_6D_6	3.98		1.89-1.77	2.02	3.98	-	3.13
4-Benzyl-*t*(4)-hydroxypiperidine2	$CDCl_3$	4.19	Same as H(5)	1.76-1.66		4.19	-	2.79
	C_6D_6	4.29		1.89-1.77		4.29	-	2.72
4-Benzyl-*t*(4)-hydroxy-3-methyl-2,6-diphenylpiperidine 3	$CDCl_3$	3.86	1.83	1.75	1.62	4.10	0.86	3.06 2.69
	C_6D_6	4.04	1.95-2.03		1.84	4.21	1.11	3.06 2.66
4-Benzyl-*t*(4)-hydroxy-3-methyl-2,6-bis- (*p*-chlorophenyl)piperidine4	$CDCl_3$	3.84	1.75	1.66	1.57	4.08	0.84	3.04 2.68
	C_6D_6	3.85	1.81-1.73		1.69	4.02	0.99	3.01 2.62
4-Benzyl-*t*(4)-hydroxy-3-methyl-2,6-di-2′-furylpiperidine6	$CDCl_3$	4.02	2.01	1.87	1.71	4.18	0.92	2.73 3.07
	C_6D_6	4.26	2.18	2.03	1.88	4.34	1.18	3.01 2.61
4-Benzyl-*t*(4)-hydroxy-3-ethyl-2,6-diphenylpiperidine7	$CDCl_3$	3.92	1.58	1.78	1.63	4.06	1.80, 1.21 (CH_2CH_3) 0.52 (CH_2CH_3)	3.15 2.66
	C_6D_6	3.88	1.47	1.70	1.57	3.91	1.78, 1.32 (CH_2CH_3) 0.59 (CH_2CH_3)	2.97 2.37
4-Benzyl-*t*(4)-hydroxy-3-ethyl-2,6-bis-(*p*-chlorophenyl)piperidine8	$CDCl_3$	3.91	1.47	1.64	1.53	4.03	1.75, 1.17 (CH_2CH_3) 0.55 (CH_2CH_3)	2.64 3.13
	C_6D_6	3.94	1.50	1.72	1.67	3.96	1.93, 1.39 (CH_2CH_3) 0.78 (CH_2CH_3)	3.16 2.58

t(4)-hydroxypiperidine **2** and 3-methyl tertiary alcohols **3** and **6** but shields all the ring protons in 3-ethyl tertiary alcohol **7**. In 4-benzyl-*c*(4)-hydroxypiperidine **1** benzylic protons [H(2) and H(6)] resonate at lower frequency whereas methylene protons at C(5)/C(3) resonate at higher frequency in C_6D_6 relative to $CDCl_3$. In 3-alkyl-*para*-chlorophenyl tertiary alcohols **4** and **8** considerable upfield and downfield shifts are observed for H(6) and methylene protons at C(5), respectively, in C_6D_6 compared to $CDCl_3$. Alkyl protons at C(3) except one of the methylene protons of ethyl group at C(3) in **7** are also deshielded in C_6D_6 compared to $CDCl_3$.

It has been previously reported that phenol forms weak hydrogen bonding with π-electrons of the benzene molecule[20]. One can also expect such OH-π interaction of C_6D_6 molecule in the present set of compounds. Among the possible rotamers for the hydroxyl group at C(4), OH-π interaction is possible only in *anti* rotamer but not in *gauche* forms. In *gauche* rotamer solvent molecules C_6D_6 cannot approach OH group freely since there will be severe interaction between solvent C_6D_6 molecule and phenyl ring of benzyl group at C(4). Specific association of solvent C_6D_6 molecule with OH group at C(4) is controlled by the steric requirements and hence the solvent molecule C_6D_6 may prefer a particular orientation in which most of the heterocyclic ring protons lie in the deshielding region of the aromatic ring of C_6D_6 molecules.

Different deshielding and shielding magnitudes observed for ring protons may be attributed to the spatial relationship between these protons and the aromatic ring. Similar differential shielding and deshielding magnitude has been observed in some steroidal ketones due to the replacement of $CDCl_3$ by C_6D_6[21,22].

Conclusion

Eight compounds of 4-benzyl-4-hydroxypiperidines were synthesized from their respective parent compounds by benzyl magnesium chloride in dry ether medium. The structures of these compounds were characterized by ^1H and ^{13}C NMR spectra recorded in $CDCl_3$. The effect of change of solvent from $CDCl_3$ to C_6D_6 and DMSO-d_6 causes appreciable changes in various protons in the compounds **1-8**. The spectral results obtained from those spectra were carefully interpreted and various effects were explained in detail.

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