Piperidine

Piperidine			
[[File:Piperidin.svg	]]	[[File:Piperidine-equatorial-3D-balls-B.png	]]
[[Image:Piperidine-3D-vdW.png		]]	
Identifiers			
CAS number	110-89-4 [1] ✓		
PubChem	8082 [2]		
ChemSpider	7791 [3] ✓		
ChEMBL	CHEMBL15487 [4] ✓		
RTECS number	TM3500000		
Jmol-3D images	Image 1 [5]		
Properties			
Molecular formula	$C_5H_{11}N$		
Molar mass	85.15 g/mol		
Appearance	colourless liquid		
Density	0.862 g/ml, liquid		
Melting point	−7 °C		
Boiling point	106 °C		
Solubility in water	miscible		
Acidity (pK_a)	11.22[6]		
Viscosity	1.573 cP at 25 °C		
Hazards			
EU classification	Flammable (**F**) Toxic (**T**)		
R-phrases	R11, R23/24, R34		
NFPA 704			
Related compounds			
Related compounds	pyridine pyrrolidine piperazine		
✓ (what is this?) (verify) [7] Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)			
Infobox references			

Piperidine (**Azinane** after the Hantzsch–Widman nomenclature) is an organic compound with the molecular formula $(CH_2)_5NH$. This heterocyclic amine consists of a six-membered ring containing five methylene units and one nitrogen atom. It is a colorless fuming liquid with an odor described as ammoniacal, pepper-like;[8] the name comes from the genus name *Piper*, which is the Latin word for pepper.[9] Piperidine is a widely used building block and chemical reagent in the synthesis of organic compounds, including pharmaceuticals.

Production

Industrially, piperidine is produced by the hydrogenation of pyridine, usually over a molybdenum disulfide catalyst:[10]

$$C_5H_5N + 3\ H_2 \rightarrow C_5H_{10}NH$$

Pyridine can also be reduced to piperidine by sodium in ethanol.[11]

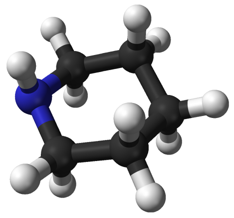
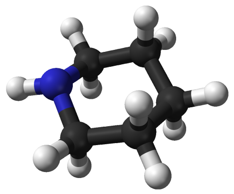
Natural occurrence of piperidine and derivatives

Piperidine itself has been obtained from black pepper,[12] from *Psilocaulon absimile* N.E.Br (Aizoaceae),[13] and in *Petrosimonia monandra*.[14]

The piperidine structural motif is present in numerous natural alkaloids. These include piperine, which gives black pepper its spicy taste. This gave the compound its name. Other examples are the fire ant toxin solenopsin,[15] the nicotine analog anabasine of the Tree Tobacco (*Nicotiana glauca*), lobeline of the indian tobacco, and the toxic alkaloid coniine from poison hemlock, which was used to put Socrates to death.[16]

Conformation

Piperidine prefers a chair conformation, similar to cyclohexane. Unlike cyclohexane, piperidine has two distinguishable chair conformations: one with the N–H bond in an axial position, and the other in an equatorial position. After much controversy during the 1950s–1970s, the equatorial conformation was found to be more stable by 0.72 kcal/mol in the gas phase.[17] In nonpolar solvents, a range between 0.2 and 0.6 kcal/mol has been estimated, but in polar solvents the axial conformer may be more stable.[18] The two conformers interconvert rapidly through nitrogen inversion; the free energy activation barrier for this process, estimated at 6.1 kcal/mol, is substantially lower than the 10.4 kcal/mol for ring inversion.[19] In the case of *N*-methylpiperidine, the equatorial conformation is preferred by 3.16 kcal/mol,[17] which is much larger than the preference in methylcyclohexane, 1.74 kcal/mol.

	
axial conformation	equatorial conformation

Reactions

Piperidine is a widely used secondary amine. It is widely used to convert ketones to enamines.[20] Enamines derived from piperidine can be used in the Stork enamine alkylation reaction.[21]

Piperidine can be converted to the chloramine $C_5H_{10}NCl$ with calcium hypochlorite. The resulting chloramine undergoes dehydrohalogenation to afford the cyclic imine.[22]

NMR chemical shifts

^{13}C NMR = ($CDCl_3$, ppm) 47.5, 27.2, 25.2
^{1}H NMR = ($CDCl_3$, ppm) 2.79, 2.19, 1.51

Uses

Piperidine is used as a solvent and as a base. The same is true for certain derivatives: *N*-formylpiperidine is a polar aprotic solvent with better hydrocarbon solubility than other amide solvents, and 2,2,6,6-tetramethylpiperidine is highly sterically hindered base, useful because of its low nucleophilicity and high solubility in organic solvents.

A significant industrial application of piperidine is for the production of dipiperidinyl dithiuram tetrasulfide, which is used as a rubber vulcanization accelerator.[10]

Otherwise piperidine and its derivatives are ubiquitous building blocks in the synthesis of pharmaceuticals and fine chemicals. The piperidine structure is e.g. found in the pharmaceuticals paroxetine, risperidone, methylphenidate, raloxifene, minoxidil, thioridazine, haloperidol, droperidol, mesoridazine, meperidine, melperone the psychochemical agents Ditran-B (JB-329), N-methyl-3-piperidyl benzilate (JB-336) and in many others.

Piperidine is also commonly used in chemical degradation reactions, such as the sequencing of DNA in the cleavage of particular modified nucleotides. Piperidine is also commonly used as a base for the deprotection of Fmoc-amino acids used in solid-phase peptide synthesis.

Piperidine is listed as a Table II precursor under the United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances due to its use (peaking in the 1970s) in the clandestine manufacture of PCP (also known as angel dust, sherms, wet, etc.).[23]

References

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