MNDO STUDY OF NITROGEN ATOM INVERSION IN PIPERAZINE, *N,N'*-DIMETHYLPIPERAZINE AND *N,N'*-DICHLOROPIPERAZINE☆

Yavari, Issa*

Department of Chemistry, Tarbiat Modarres University, P.O. Box 14155-4838, Tehran, I.R. Iran.

Nori-Shargh, Davood; Fallah-Bagher-Shaidaii, Hossein and Dadgar, Mohsen

Department of Chemistry, Science and Research Branch, Islamic Azad University,
P.O. Box 19395-1775, Tehran, Iran.

ABSTRACT: *MNDO semi-empirical SCF MO calculations are used to study the pyramidal nitrogen atom inversion and configurational equilibria in the title compounds.*

KEY WORDS: *MNDO calculations, Nitrogen inversion, Stereochemistry, Conformational analysis.*

INTRODUCTION

Monocyclic six-membered ring nitrogen hetero-cycles are an exteremely important class of compounds which occur in a range of natural and un-natural products [1,2]. Configurational properties of piperazine (1) have aroused considerable interest, largely because of the interesting interplay of steric and electronic effects upon barriers and inversion equilibria at the nitrogen atoms [3,4]. Understanding of the configurational equilibria involved in piperazine and its *N,N'*-disubstituted derivatives has been slow to develop, largely because of the lack of experimental techniques which can directly observe and identify different configurations, namely, EE, EA and AA.

Theoretical calculations have been reported for the three energy-minimum conformations of piperazine (1). Ab initio studies at the 3-21G [5] and 4-21G [6] levels indicated that for the parent piperazine the EE conformation is the most stable, with the EA only 1.8-2.9 kJ mol^{-1} higher in energy and the AA geometry 4.9-7.5 kJ mol^{-1} above the EE configuration. While the EE form is calculated to be the most stable geometry by molecular mechanics (MM2) calculations, [7] similar strain energies are obtained for the EA and AA configurations by this method.
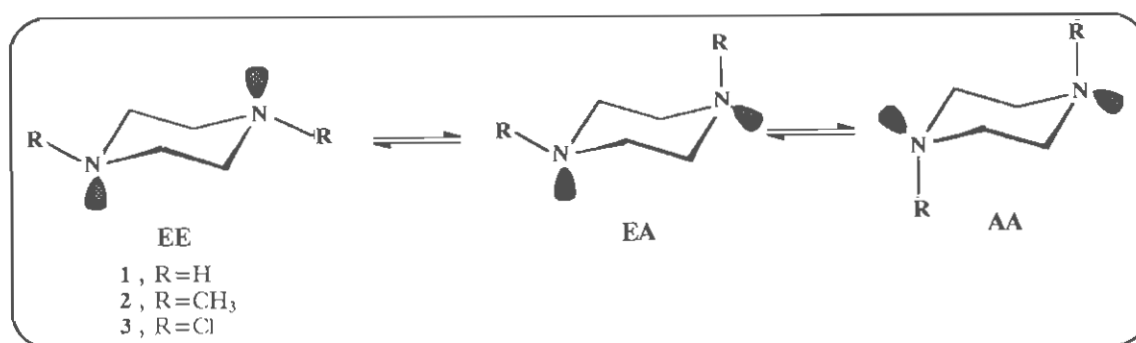
We wish to report a detailed MNDO (Modified

EE
EA
AA
1 , R=H
2 , R=CH₃
3 , R=Cl

Neglect of Diatomic Overlap) [8] study of pyramidal nitrogen atom inversion and configurational equilibria in piperazine (1), *N,N'*- dimethylpiperazine (2) and *N,N'*-dichloropiperazine (3).

CALCULATIONS

Semi-empirical calculations were carried out using the MNDO method with the MOPAC 6.0 program [9,10] implemented on a VAX-4000-300 computer. Energy-minimum geometries were located by minimizing energy, with respect to all geometrical coordinates and without imposing any symmetry constraints. The structures of the transition-state geometries were obtained using the optimized geometries of the equilibrium configurations and the procedure of *Dewar* et al. [11] (Keyword Saddle). We have checked that all of the configurations obtained in the present work are true local energy minima and energy maxima, as evidenced by the fact that they are calculated to have 3N-6 and 3N-7 real vibrational frequencies, respectively [12,13].

RESULTS AND DISCUSSION
Piperazine (1)

Piperazine and its simple derivatives such as 2 and 3 exist almost exclusively in chair conformation [3,4]. The most stable configuration of 1 is calculated to be the diequatorial, 1-EE, in agreement with electron diffraction [14], dipole-moment and infrared studies [15]. The standard strain energies ($\Delta\Delta H_f^o$) of the equatorial-axial (1-EA) and diaxial (1-AA) configurations are 5.56 and 9.50 kJ mol⁻¹, respectively. (The standard strain energy in each geometry of a molecule is defined as the difference between the standard heats of formation, ΔH_f^o , for that geometry

and the most stable conformation of the molecule [16]). The calculated strain energy for 1-EA configuration is higher than the value (about 2 kJ mol⁻¹) estimated from IR measurements [15]. The structural parameters of 1-EE, 1-EA and 1-AA configurations, given in Table 1, show variations which could be attributed to anomeric effect [17] as have been observed in other molecules with L_p-N-C-C arrangements. When the C-C bond is antiperiplanar to the lone pair of the nitrogen atom, the bond is stretched and the angle N-C-C is widened. As shown in Table 1, the C-C bonds are longer in 1-AA than in 1-EE. The N-C-C angles are also wider in 1-AA configuration.

Using *Dewar* et al. [11] SADDLE procedure we studied the transition-state geometries (1-EE → 1-EA)# and (1-EA → 1-AA)# for pyramidal nitrogen atom inversion [18] in 1-EE and 1-EA configurations, respectively. The barrier for nitrogen inversion in piperazine is not known, but it is predicted to be close to the value (25.5 kJ mol⁻¹) reported for piperidine [19]. In fact, the calculated barriers for *N*-inversion in piperazine are in good agreement with that observed for piperidine (see Table 1). The C-N bond lengths of the nitrogen atom which is undergoing pyramidal inversion in saddle geometries are about 0.02 to 0.03 Å shorter than the corresponding ground state configurations, presumably because of the change in hybridization of the nitrogen atom.

N,N'-*Dimethylpiperazine* (2)

The geometrical features of 2, shown in Table 2, are similar to those of the parent heterocycle piperazine. In this case the most stable configuration is 2-EE in agreement with kinetically controlled

Table 1: Calculated structural parameters and energies (k J mol⁻¹) in various geometries of piperazine (1)

Feature	EE	EA	AA	(EE → EA)#	(EA → AA)#
Bond lengths (Å)					
$r_{1,2}$	1.467	1.467	1.469	1.469	1.444
$r_{2,3}$	1.545	1.549	1.551	1.552	1.554
$r_{3,4}$	1.467	1.469	1.469	1.444	1.469
Bond angles(°)					
θ_{612}	116	117	116	117	122
θ_{123}	111	112	115	111	112
θ_{234}	111	114	115	111	112
θ_{345}	116	115	116	121	116
Dihedral angles(°)					
ϕ_{6123}	51	50	42	51	43
ϕ_{1234}	−49	−46	−41	−45	−40
ϕ_{2345}	51	44	42	48	42
ϕ_{H123}	176	174	−82	175	−135
ϕ_{H456}	−176	80	82	−132	82
Dipole moment[a]	0.0	2.0	0.0	1.4	1.2
ΔH_f°	−17.28	−11.72	−7.78	6.70	9.59
$\Delta \Delta H_f^\circ$	0.00	5.56	9.50	23.98	26.78
Expt.[b]	0.0	2	—	—	—

a : In units of Debye

b : Ref [15]

protonation studies [20]. The equatorial-axial configuration, **2-EA**, is calculated to be 8.45 kJ mol⁻¹ less stable than **2-EE**. The free-energy difference between an axial and an equatorial N-methyl group in **2**, under kinetically controlled conditions at room temperature, is estimated to be 12.4 kJ mol⁻¹ [20]. The agreement between this and the calculated value is fairly good. The calculated strain energy ($\Delta\Delta H_f^\circ$) for the diaxial geometry, **2-AA**, is 16.4 kJ mol⁻¹ and it is not expected to be populated to a significant amount at room temperature. The calculated barriers for pyramidal inversion of the nitrogen atoms in **2** are lower than the corresponding barriers in piperazine. Barrier to N-inversion in **2** have not been experimentally determined. It would be valuable, of course, to have direct experimental data on N-

inversion in **2** for comparison with results of the MNDO calculations.

N,N'-Dichloropiperazine (3)

The results of the MNDO studies of the mobile inversion equilibrium at the nitrogen atoms in **3** are shown in Table 3. The diequatorial configuration, **3-EE**, is calculated to be the most stable geometry. The **EE** and **EA** free-energy difference for **3** has been shown by ¹³C NMR spectroscopy to be about 2 kJ mol⁻¹ [21]. The standard strain energy of the equatorial-axial configuration of **3** is calculated to be 4.48 kJ mol⁻¹, in fairly good agreement with the NMR measurements [21]. Since the calculated strain energy for the diaxial configuration, **3-AA**, is only 10.26 kJ mol⁻¹ above **3-EE**, it is expected to be populated to a small

Table 2: Calculated structural parameters and energies (kJ mol^{-1}) in various geometries of N,N'-dimethylpiperazine *(2)*

Feature	EE	EA	AA	(EE → EA)[#]	(EA → AA)[#]
Bond lengths(Å)					
$r_{1,2}$	1.469	1.468	1.469	1.469	1.457
$r_{2,3}$	1.547	1.551	1.552	1.551	1.553
$r_{3,4}$	1.469	1.469	1.469	1.457	1.469
Bond angles(°)					
θ_{612}	115	116	115	116	119
θ_{123}	112	112	114	112	113
θ_{234}	112	114	114	112	115
θ_{345}	115	114	115	117	114
Dihedral angles(°)					
ϕ_{6123}	51	48	46	50	40
ϕ_{1234}	–50	–47	–46	–47	–52
ϕ_{2345}	51	48	51	49	47
ϕ_{H123}	171	172	–94	172	–135
ϕ_{H456}	–171	96	94	–126	96
Dipole moment[a]	0.0	1.4	0.0	1.0	0.6
ΔH_f°	17.92	26.37	34.32	30.31	36.88
$\Delta \Delta H_f^\circ$	0.00	8.45	16.40	12.39	18.96
Exptl[b]	0.0	12.4	—	—	—

a : In units of Debye
b : Ref [20]

Table 3: Calculated structural parameters and energies (k J mol^{-1}) in various geometries of N,N'-dichloropiperazine *(3)*

Feature	EE	EA	AA	(EE → EA)[#]	(EA → AA)[#]
Bond lengths(Å)					
$r_{1,2}$	1.480	1.480	1.481	1.481	1.453
$r_{2,3}$	1.459	1.550	1.547	1.555	1.553
$r_{3,4}$	1.480	1.480	1.481	1.454	1.482
Bond angles(°)					
θ_{612}	114	115	114	115	122
θ_{123}	110	110	116	110	110
θ_{234}	110	116	116	109	116
θ_{345}	114	114	114	121	115
Dihedral angles(°)					
ϕ_{6123}	55	56	42	56	48
ϕ_{1234}	–52	–48	–42	–49	–43
ϕ_{2345}	55	43	42	50	42
ϕ_{H123}	178	179	–84	179	–131
ϕ_{H456}	–178	83	84	–131	84
Dipole moment[a]	0.0	0.3	0.0	1.2	1.2
ΔH_f°	137.05	141.53	147.31	174.14	179.29
$\Delta \Delta H_f^\circ$	0.00	4.48	10.26	37.09	42.24
Exptl[b]	0.0	2	—	56.5	—

a : In units of Debye
b : Ref [21]

extent at room temperature.

Electron attraction away from nitrogen along a σ bond is known to increase the pyramidal inversion barrier [18]. The free-energy of activation for EE to EA conversion which involves N-inversion, has been shown by ^{13}C NMR spectroscopy to be 56.5 kJ mol^{-1} The calculated barrier by MNDO method is about 20 kJ mol^{-1} lower than the experimental value.

In conclusion, MNDO calculations show that the EE configuration is the most stable geometry for compounds **1-3**, in agreement with available experimental results. Compounds **1** and **3** are expected to exist as a mixture of **EE**, **EA**, and to a small extent, **AA** configurations at room temperature. Compound **2** should be configurationally more homogeneous. The predicted barriers for N-inversion in **1-3** are about 10-20 kJ mol^{-1} lower than the experimental values for these compounds.

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