CONFORMATIONAL STUDY OF N-CHLOROPIPERAZINES

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Abstract – Four N-chloropiperazines [1,4-dichlro-*trans*-2,5-dimethylpiperazine, 1-chloro-4-(4-nitrophenyl)piperazine, 1-chloro-4-phenylpiperazine and 1-chloro-4-(2-methoxyphenyl) piperazine] are conformationally studied by ^{13}C DNMR. *Ab initio* energy minimisations and geometry optimisations were also carried out on these compounds and on 1,4-dichlropiperazine using the PCM model at the HF/6-31G* level. Results are discussed in terms of previous related work.

Introduction

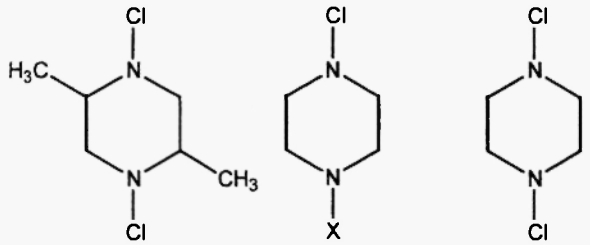
Piperazines, like most other six-membered saturated nitrogen heterocycles are flexible molecules where both ring and nitrogen inversion can occur. Past conformational studies on piperazines have been mainly centred on N-alkyl, ring alkyl or ring heterosubstituted derivatives.

Studies on nitrogen heterosubstituted derivatives are indeed more rare. One such derivative of piperazine already studied is 1,4-dichloropiperazine (5) for which the free energy difference was found to be $\Delta G^0_c = 0.5$ kcal.mol^{-1} in favour of the diequatorial *vs* equatorial:axial conformer (1).

The previous ΔG^0_c value reflects an abnormal conformational equilibrium when compared with $\Delta G^0_c = 1.5$ kcal.mol^{-1} in favour of the equatorial *vs* axial conformer of 1-chloropiperidine (2). Similar behaviour is also displayed by *trans*-1,4-dichlorocyclohexane (3) relative to chlorocyclohexane (4). The equatorial conformer of chlorocyclohexane is preferred by 0.6 kcal.mol^{-1} while for *trans*-1,4-dichlorocyclohexane the diequatorial conformer is preferred over the diaxial by only 0.2 kcal.mol^{-1} instead of the expected 1.2 kcal.mol^{-1} if ΔG^0_c values where additive.

The solvent dependence of equilibrium in the case of 1,4-dichlorocyclohexane and the solvent independence of equilibrium in the case of the 1,4-dichloropiperazine lead to two different interpretations of the observed phenomena. The extra stabilization of the diaxial conformer of *trans*-1,4-dichlorocyclohexane was attributed to attractive electrostatic interactions between the the axial halogen atoms and the positively charged 1,3-*syn*-axial hydrogen atoms (3), while for 1,4-dichloropiperazine the extra stabilization of the equatorial:axial *vs* the diequatorial conformer was attributed to the generalized anomeric effect (1).

The structures of the N-chloropiperazines studied (1 – 4) and of 1,4-dichloropiperazine (5) are represented in **Scheme 1**. In compound 1 both *trans* - 2,5 methyl groups are assumed to have equatorial orientation. The 4 - aryl groups in compounds 2 – 4 are also assumed to have equatorial orientation and were so chosen to modify the electronegativity of the respective nitrogen atom which is expected to decrease in the order 2 →3 → 4 as a result of the different electronic properties of the substituents.



1 2 - X = 4-nitrophenyl 5
3 - X = phenyl
4 - X = 2-methoxyphenyl

Scheme 1 – Compounds studied (1 – 5)

Results and Discussion

The room temperature ^{13}C NMR spectrum of 1,4-dichloro-*trans*-2,5-dimethylpiperazine (1) shows the three signals expected for "fast" ring and nitrogen inversion: δ 67.8 ppm ($C_{2,5}$), δ 64.4 ppm ($C_{3,6}$) and δ 18.0 ppm (CH_3). However, at this temperature signals are already broad, specially those at 67.8 and 64.4 ppm. On decreasing temperature all siganls coalesce and reappear as two uniqual sets (**Table 1**). In the ring carbon region at 233 K, four well resolved peaks can be seen: two major peaks at δ 68.7 ppm and δ 65.8 ppm and two minor peaks at δ 62.0 ppm and δ 58.1 ppm. At this temperature, if both ring and nitrogen inversion are processes to be considered, they must have been " slowed down " and the observed signals are originated from discrete conformations present in equilibrium (**Figure 1**).

Two different interpretations can be given to explain the above results:

i) Since the ring carbon atoms region only presents two sets of two signals each, from symmetry reasons the two conformers in equilibrium must come from the group 1ee, 1aa, 1'aa, 1'ee. Considering equilibrium data for 1,4-dichloropiperazine and the fact that the two minor signals appear at higher field (1), the major conformer must be 1ee. The peak at δ 68.7 ppm is assigned to $C_{2,5}$ and the peak at δ 65.8 ppm is assigned to $C_{3,6}$. The minor conformer is one of the other three of the previous group.

ii) The *trans* methyl groups at C_2 and C_5 are equatorial and prevent ring inversion so that conformers 1'aa, 1'ae and 1'ee are not present in equilibrium. Thus, the dynamic phenomenon " slowed down " is nitrogen inversion and the equilibrating conformers are 1ee and 1ae or 1aa (**Figure 1**). The two major signals are assigned to 1ee as described above. Conformer 1aa must also be excluded from being present in equilibrium

Table 1 ^{13}C chemical shift assignments for 1,4-dichloro- *trans* -2,5-dimethylpiperazine (1)[a]

Conformer	C_2	C_3	C_5	C_6	C-CH_3
1ee ø 1ae[b]	67.8	64.4	67.8	64.4	18.0
1ee[c]	68.7	65.8	68.7	65.8	18.2
1ae[c]	65.8	58.1	62.0	62.0	17.9; 17.3

[a] In $CDCl_3$ with TMS as internal reference; [b] 273 K; [c] 233K

because integration of the two minor peaks gives a ratio of 2:1 as a consequence of overlapping (of C_5 and C_6) (**Table 1**). Since conformer 1ae must have four signals for the ring carbon atoms a second overlap of two signals has to be considered (of C_2 of 1ae and C_3 of 1ee) (**Table 1**).

We assume interpretation ii). In fact, equilibrium data for methylcyclohexane (5) (ΔG^0_c = 1.8 kcal.mol^{-1}) and for 3-methylpiperidine (6)(ΔG^0_c = 1.5 kcal.mol^{-1}, despite removal of one *syn*-axial hydrogen) favouring the equatorial C-methyl conformers are a supporting argument for excluding conformers 1'aa, 1'ae and 1'ee: in each conformer we would have two such *syn*-axial CH_3/H interactions. In addition, one *syn*-axial interaction between CH_3 and Cl in 1'ae and two in 1'aa are also expected to be highly destabilizing. Considering the overlapp of the C_2 and C_5 signals of 1ae with those of $C_{3,6}$ of 1ee and C_6 of 1ae, respectively, peak weight integration of the 233 K ^{13}C NMR spectrum gives ΔG^0_c = 0.6 kcal.mol^{-1} in favour of 1ee *vs* 1ae.

For compounds 2 - 4 it is assumed that the bulky N(4)-aryl substituents are equatorially orientated so that only two conformations need to be considered: one with both chlorine and aryl groups equatorials (ee) and the other with chlorine axial and aryl equatorial (ae). These conformations interconvert by N_1-Cl inversion.

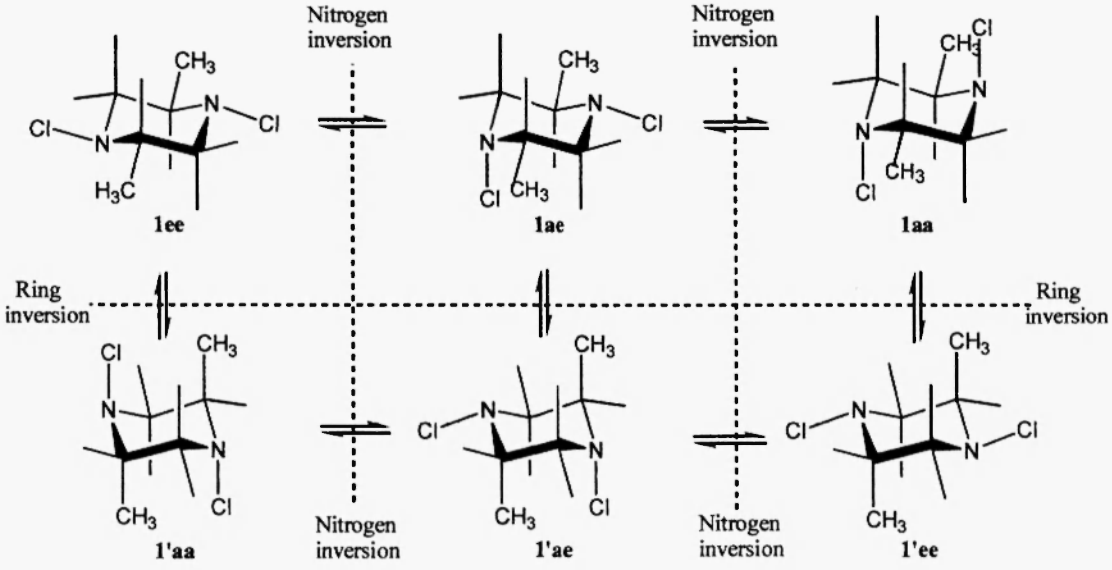


Figure 1 – Conformational interconvertions in 1,4-dichloro-*trans*-2,5-dimethylpiperazine (1)

The room temperature spectrum of each compound has the expected two peaks for the ring carbon atoms (**Table 2**).

No changes were observed in the spectra of compound 2 on decreasing temperature down to 220 K. Since in this temperature range nitrogen inversion should have been " slowed down " we conclude that we are in presence of a biased equilibrium in favour of the diequatorial conformer (2ee).

Compounds 3 and 4 showed a broadening and resharpening of their ring carbon atom signals as temperature is decreased from room temperature to *ca.* 213 K and no signals attributable to a minor conformation were observed in the low temperature spectra. Application of the Anet equations (7) allowed determination of the free energy difference ΔG°_{c} (favouring ee relative to ae conformers) and of the two half-barriers: diequatorial to transition state ($\Delta G^{\#}_{ee \rightarrow ts}$) and axial:equatorial to transition state ($\Delta G^{\#}_{ae \rightarrow ts}$) (**Table 2**).

Conclusions

Experimental results for 1 gave $\Delta G^{0}_{c} = 0.6$ kcal.mol^{-1} in favour of 1ee *vs* 1ae. The previous value is slightly higher than the one determined for the corresponding equilibrium in 1,4-dichloropiperazine (5) (1) ($\Delta G^{0}_{c} = 0.5$ kcal.mol^{-1}) showing that there is a shift of the equilibrium towards the 1ee conformer. This is contrary to the observed in 1- chloro - 2-methylpiperidines (8) for which it has been verified that the equatorial α-methyl groups increase the preference of the N-chloro group for the axial orientation.

For the series of compounds 2, 3 and 4 (**Table 2**), experimental results show that ΔG^{0}_{c} (favouring the diequatorial conformers ee) decrease in the order 2 → 3 → 4. Since the electronegativity of the N_4 nitrogen atom decreases in the same order this is the reverse of the expected order if only electronic interactions between the axially oriented N-chloro group and the *syn*-axial hydrogen atoms at C_3 and C_5 were responsible for the conformational equilibrium.

In order to find an explanation for the above facts, *ab initio* calculations (energy minimisations and geometry optimisations) were preformed for compounds 1-5 in solution using the PCM model at the HF/6-31G* level (9). Calculated and experimental results for conformational equilibria are presented in **Table 3**.

It can be concluded from the above results that, in agreement with experiment, *ab initio* calculations give for all compounds the diequatorial conformer as the more stable. Quantitatively the agreement is also very good, except for compound 4. However, it must be pointed out that, in this model compound, the methoxyl substituent is at the 2-position of the phenyl ring where it can still have a strong attractive inductive effect over the N_4 atom.

Table 2 – ^{13}C DNMR results for compounds 2, 3 and 4

Compound		2	3	4
δ (ppm)	$C_{2,6}$	62.4	62.7	63.4
(273 K)	$C_{3,5}$	48.4	50.4	51.8
$\Delta\omega_{1/2}$ max. (Hz)[a]		-	5	16
T_c (K)		-	236	233
ΔG^0_c (kcal.mol^{-1})[b]		> 1.6	1.6	1.0
$\Delta G^{\#}_{ee\rightarrow ts}$ (kcal.mol^{-1})[c]		-	12.1	11.4
$\Delta G^{\#}_{ae\rightarrow ts}$ (kcal.mol^{-1})[c]		-	10.5	10.4

[a] $\Delta\omega_{1/2}$ – maximum broadening at half height of $C_{3,5}$ signal at coalescence (T_c); chemical shift difference between $C_{3,5}$ of ee and ae conformers estimated from 5 (1); [b] ±0.1 kcal.mol^{-1}; [c] ±0.2 kcal.mol^{-1}.

Table 3 – Experimental and calculated ΔG^0_c for compounds 1, 2, 3, 4 and 5

Compound	Experimental ΔG^0_c (kcal.mol^{-1})[a]	Calculated ΔG^0_c (kcal.mol^{-1})[b]
5	0.5[c]	0.62
1[d]	0.6	0.65
2[e]	>1.6	1.84
3[f]	1.6	1.66
4[g]	1.0	1.80

[a] ±0.1kcal.mol^{-1}, ee conformers preferred; [b] ±0.01 kcal.mol^{-1}, ee conformers preferred; [c] Experimental data from (6); [c,d] In $CHCl_3$, entropy corrected; [e,f,g] In Et_2O.

Neither the trend in experimental or calculated values for equilibrium along the series of compounds 2-4 is the expected one. This fact clearly demonstrates that, on planning models for conformational studies, the fine balance between steric and electronic effects that determine conformational preferences must be taken into account. Indeed, geometry optimisations for the titled compounds using the same PCM model at the HF/6-31G* level show that there is a marked flattening of the piperazine ring at the N_4 atom that causes generalized distortions throughout the whole ring. These distortions affect both angles and bond lenghts and from them no simple explanation could be drawn for the observed trend in equilibria. However the flattening of the ring in compounds 2-4 might explain that nitrogen inversion half-barriers for these compounds (**Table 2**) are smaller than for 1,4-dichloropiperazine (5) ($\Delta G^{\#}_{ee\rightarrow ts}$ = 14.0 kcal.mol^{-1} and $\Delta G^{\#}_{ae\rightarrow ts}$ = 13.5 kcal.mol^{-1}) (1).

Experimental

Synthesis of Compounds – Compound 1 was prepared by addition of N-chlorosuccinimide (1.40 g, 0.01 mole) in 20 ml of dry ether to a solution of *trans*-2,5-dimethylpiperazine (0.58 g, 0.005 mole) in 50 ml of dry ether. After 4 hr stirring the mixture was extracted with 50 ml of diluted sulfuric acid, the organic layer dried over anhydrous sodium sulfate and the solvent evaporated on rotary to yield 0.42 g (70%) of product.

Compounds 2, 3 and 4 were similarly prepared from reaction of equimolar amounts of NCS and of the parent piperazines in dry ether, under ice cooling. Due to their instability, the compounds were obtained with enough purity for spectroscopic studies by repetitively filtering off the succinimide formed and concentrating the ethereal solution.

All compounds were characterized by their ^{1}H (90 MHz) and ^{13}C (22.5 MHz) NMR and Mass Spectra (EI, 70 eV). In the MS spectra the compounds showed the relationship of molecular ion peaks characteristic of the presence of two (for 1) or one (for 2, 3 and 4) chlorine atoms.

Variable Temperature ^{13}C DNMR Studies – Compounds were studied in 10% solutions in a JEOL90Q NMR Spectrometer equipped with a variable temperature unit, using å 10mm sample tubes and TMS as internal reference. Compound 1 was studied in $CDCl_3$ and compounds 2, 3 and 4 in Et_2O with $(CD_3)_2CO$ in a sealed capillary tube as lock. Spectra were recorded from or near room temperature down to *ca.* 30 K below coalescence temperature.

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