CONFORMATIONAL STUDY OF N-HALOPIPERIDINES

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Abstract - Conformational equilibria and nitrogen inversion barriers are determined by ^{13}C DNMR for three 1-chloropiperidines (1-chloro-2-methylpiperidine, 1-chloro-*cis*-2,6-dimethylpiperidine and 1-chloro-2-ethylpiperidine) and three 1-bromopiperidines (1-bromopiperidine,1-bromo-2-methylpiperidine and 1-bromo-*cis*-2,6-dimethylpiperidine). Experimental results are discussed and rationalised for all compounds studied and correlated with previous work.

Introduction

Six-membered saturated cyclic compounds are flexible molecules that have attracted the attention of chemists since the advent of conformational analysis until today.

Particularly interesting within this group of compounds are nitrogen heterocycles where both ring and nitrogen inversion can occur. The large volume of experimental work produced on these compounds allowed the understanding of the main features of their conformational analysis presently included in the contents of general Organic Chemistry texts (1): rings even with more than one methylene unit substituted by heteroatoms continue to prefer chair conformations; nitrogen or ring alkyl substituents tend to prefer equatorial orientations; the preference of substituents for the equatorial orientation increases with the size of the alkyl group; nitrogen inversion has lower free energy of activation than ring inversion. However, past studies have been almost exclusively directed to ring and/or nitrogen substituted alkyl derivatives.

Studies concerning six-membered saturated nitrogen heterocycles with nitrogen and/or ring polar substituents are more rare despite the fact that these groups introduce interesting additional electronic effects in the molecule. The still controversial anomeric and associated stereoelectronic effects (2, 3) are representative examples. Another consequence of the introduction of electronegative groups on the inverting nitrogen atom is the increase of the barrier for pyramidal atomic inversion (4). In fact, for the sp^3 hybridized nitrogen atom to invert it must pass through an sp^2 hybridized transition state with less p character in the bonding orbitals. Electronegative substituents on nitrogen will also increase these barriers by increasing the p character of its bonding orbitals.

Two compounds of this group already studied by ^{13}C DNMR are 1-chloropiperidine 1 and 1,4-dichloropiperazine 9. The free energy difference ΔG^0_c was found to be 1.5 kcal.mol^{-1} for 1-chloropiperidine (5) (in favour of the equatorial *vs* axial conformer) and 0.8 kcal mol^{-1} for 1,4-dichloropiperazine (6) (in favour of the diequatorial *vs* equatorial:axial conformer). These values demonstrate that there is an increased preference for the axial orientation of the chlorine substituent relative to the methyl groups of the analogues 1-methylpiperidine (7) (8, ΔG^0_c = 2.7 kcal.mol^{-1} in favour of

the N-methyl equatorial conformer) and 1,4-dimethylpiperazine (8) (10, ΔG^0_c > 2.6 kcal.mol^{-1} in favour of the diequatorial conformer) due to its lower steric requirements. As expected it was determined that nitrogen inversion for compounds 1 and 9 has higher barriers than for 8 and 10 but is still the lower free energy inversion process despite this increase.

Conformational equilibria for compounds 2 and 3 were also studied by variable temperature ^{1}H NMR (9). ΔG^0_c = 1.2 and 0.7 kcal.mol^{-1} in favour of the N-chlorine equatorial conformers, respectively were determined despite overlapping of signals due to the major and minor conformers below coalescence.

The set of 1-chloro and 1-bromopiperidines whose conformational analysis study by ^{13}C DNMR is described here was devised not only to verify experimentally the legitimacy of extrapolation of conclusions drawn for their N-alkyl analogues but also to provide results that are essential for theoretical studies. The bromine compounds, to the best of our knowledge, are novel derivatives.

Experimental

Synthesis of Compounds – Compounds were prepared by a modified technique of N-halogenation of the parent piperidines (10) with the corresponding N-halosuccinimide in dry ether (11), and characterised by their ^{1}H (90 MHz) and ^{13}C (22.5 MHz) NMR and Mass Spectra (EI, 70 eV). In the MS spectra the haloamines showed the relationship of molecular ion peaks characteristic of the presence of chlorine or bromine.

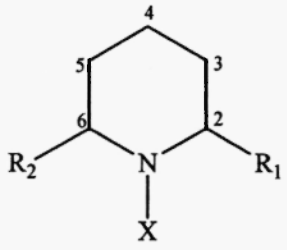
Variable Temperature ^{13}C DNMR Studies – Compounds were studied in 10% $CDCl_3$ solutions in a Jeol FX90Q NMR Spectrometer equipped with a VT unit, using ϕ 10mm sample tubes and TMS as internal reference. Spectra were recorded from or near RT down to *ca.* 30 K below coalescence temperature.

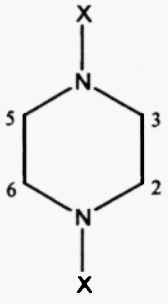
Results and Discussion

The structural formulae of the N-halopiperidines studied conformationally (2 – 7) and of the related compounds brought into discussion (1, 8 – 10) are presented in **Scheme 1**.

For compound 5, whose ring is unsubstituted by alkyl groups it is assumed that nitrogen inversion has lower free energy of activation than ring inversion (5,6); for the other compounds it is assumed that the ring alkyl substituents are equatorial and that they prevent ring inversion (9). So, in all cases only two conformers are present in equilibrium (one with the N-halogen equatorial and the other with the N-halogen axial) and changes in the low temperature ^{13}C spectra attributable to the slowing down of a dynamic phenomenon are only observed when nitrogen inversion is "stopped" in the NMR time scale. These changes are of two types: i – Compounds whose conformational equilibria are biased show a broadening and resharpening of signals in the ^{13}C spectra as temperature is gradually decreased. When resharpening occurs the equilibrium population of the minor conformer has decreased to an extent that its signals are generally not observed. Application of the Anet equations (12) allows determination of the free energy difference ΔG^0_c and of the two half-barriers: equatorial conformer to transition state ($\Delta G^{\#}_{c\rightarrow ts}$) and axial conformer to transition state ($\Delta G^{\#}_{a\rightarrow ts}$). ii – Compounds that have considerable populations (*ca.* 10% or more) of the two conformers at equilibrium show signals for both in the ^{13}C spectra below coalescence temperature. For these compounds ΔG^0_c was determined by integration of signals and $\Delta G^{\#}_{c\rightarrow ts}$ and $\Delta G^{\#}_{a\rightarrow ts}$ by application of the Gutowski-Holm (13) and Bovey *et al.* equations (14).

Analysis of experimental results for nitrogen inversion was made considering the two "half-barriers" (e→ts and a→ts)(7,15).





1 $R_1 = R_2 = H$; X = Cl
2 $R_1 = CH_3$; $R_2 = H$; X = Cl
3 $R_1 = R_2 = CH_3$, *cis*; X = Cl
4 $R_1 = CH_2CH_3$; $R_2 = H$; X = Cl
5 $R_1 = R_2 = H$; X = Br
6 $R_1 = CH_3$; $R_2 = H$; X = Br
7 $R_1 = R_2 = CH_3$, *cis* ; X = Br
8 $R_1 = R_2 = H$; X = CH_3

9 X = Cl
10 X = CH_3

Scheme 1 Compounds studied (2 – 7) and discussed (1, 8, 9 and 10)

On the variable temperature ^{13}C NMR probe the slowing down of nitrogen inversion is observed for all compounds under study. For compounds 2, 3, 4, 6 and 7 the spectra are already broad at room temperature. All signals, especially those assigned to C_2 and C_3, broaden on lowering temperature, go across coalescence and finally resharpen at still lower temperatures.

For all compounds, except 5, below coalescence two unequal sets of signals were observed in the spectra indicating the presence of two conformations in equilibrium. Based on the conformational study of other N-halopiperidine derivatives (5, 6) the major conformer was assigned to the N-halo equatorial conformer and the minor one to the N-halo axial conformer; this assignment gave a good correlation of chemical shifts (**Table 1**). Integration of the low temperature spectra gives ΔG^0_C and application of the Gutowski – Holm (13) and Bovey *et al.* equations (14) gives $\Delta G^{\#}_{e \to a}$ and $\Delta G^{\#}_{a \to e}$.

For compound 5, that did not show signals attributable to the minor N-halo axial conformer in the low temperature NMR spectra, equilibrium and activation free energies were determined by the Anet equations (12).

Conclusions

^{13}C NMR chemical shifts and assignments for the parent piperidines and for compounds 1 – 7 at fast and slow exchange are presented in **Table 1**.

A summary of equilibria and nitrogen inversion free energies as well as room temperature conformer populations for the series of compounds studied (2 – 7) and for 1-chloropiperidine (1) (5) is presented in **Table 2**.

Equilibrium data show a similar trend for chlorine (1→2→3,4) and bromine (5→6→7) compounds: the introduction of equatorial alkyl groups in the 2 and 2,6-*cis* positions gradually shifts the equilibrium towards the 1-halopiperidine axial conformer. This effect, well established for alkyl substituents (7), also applies in the present case. Interestingly, conformational equilibrium data are very similar for both the chlorine and bromine series despite the

slightly larger Van der Waals radii of bromine relative to chlorine. This difference in size of substituents is not enough to make a significant difference in ΔG^0_e. However, a significant difference is found when we compare equilibrium data

Table 1 ^{13}C NMR spectral data for compounds 1 – 7[a] and their parent amines

Compound	C_2	C_3	C_4	C_5	C_6	$C_{1'}$	$C_{2'}$
Piperidine	47.5	27.2	25.2	27.2	47.5	-	-
2-Methylpiperidine	52.5	34.9	25.1	26.4	47.3	23.2	-
2,6-cis-Dimethylpiperidine	52.6	34.2	25.0	34.2	52.6	23.2	-
2-Ethylpiperidine	58.6	32.6	25.0	26.7	47.3	30.2	10.4
1[b]	64.3	28.0	23.0	28.0	64.3	-	-
1e	64.5	28.4	23.0	28.4	64.5	-	-
1a	59.7	20.4	-	20.4	59.7	-	-
2	66.2	35.1	24.0	27.4	64.0	21.6	-
2e	66.4	35.5	23.9	28.2	64.5	22.0	-
2a	61.7	32.1	-	-	59.8	19.9	-
3	66.8	35.5	24.0	35.5	66.8	22.3	-
3e	67.0	35.8	24.0	35.8	67.0	22.7	-
3a	63.2	31.5	-	31.5	63.2	20.5	-
4	71.0	30.6	26.4	27.4	63.8	24.1	9.4
4e	71.4	31.8	27.3	28.0	64.8	23.8	9.0
4a	67.6	23.8	-	20,2	59.9	20.2	10.6
5[c]	65.9	28.8	23.0	28.8	65.9	-	-
5e	65.8	28.7	23.0	28.8	65.8	-	-
6	67.4	34.8	24.2	28.0	66.5	23.7	-
6e	67.5	35.8	24.2	29.3	66.8	24.2	-
6a	63.1	32.9	-	22.8	62.8	20.6	-
7e	68.2	35.9	25.0	35.9	68.2	23.9	-
7a	63.9	27.5	22.7	27.5	63.9	20.0	-

[a] In $CDCl_3$; TMS as reference; e – N-halo equatorial conformer; a – N-halo axial conformer
[b] Data from reference (4); [c] N-halo axial conformer not observed

for the N-halopiperidines with those for the N-alkylpiperidine analogues (7,15), where stronger 1,3-*syn*-axial interactions lead to much smaller N-methyl axial populations.

Table 2 Equilibrium and activation free energies and room temperature populations for compounds 1 – 7

Compound	$\Delta G^{\ddagger}_{e\rightarrow ts}$ [a] (kcal.mol^{-1})	$\Delta G^{\ddagger}_{a\rightarrow ts}$ [a] (kcal.mol^{-1})	ΔG^{0}_{e} [b] (kcal.mol^{-1})	Population ratio(e:a) (25°C)
1[c]	11.7	10.2	1.5	93:7
2[d]	13.4	12.3	1.1	87:13
3[e]	14.7	13.8	0.9	82:18
4[f]	13.9	13.2	0.7	77:23
5[g]	11.0	9.5	1.5	93:7
6[h]	13.3	12.1	1.2	88:12
7[i]	14.6	13.8	0.8	80:20

[a] ±0.2 kcal.mol^{-1}; [b] ±0.1 kcal.mol^{-1}; [c] Data from reference (4); [d] For C_2: T_c = 260 K and $\Delta\nu_{ae}$ = 106 Hz; [e] For C_2: T_c = 288 K and $\Delta\nu_{ae}$ = 86 Hz; [f] For C_2: T_c = 278 K and $\Delta\nu_{ae}$ = 110 Hz; [g] For C_5: T_c = 207 K, maximum broadening at half-height $\Delta\omega_{1/2}$ = 5 Hz and $\Delta\nu_{ae}$=180 Hz (estimated from 1); [h] For C_3: T_c = 262 K and $\Delta\nu_{ae}$ = 65 Hz; [i] For C_2: T_c = 289 K and $\Delta\nu_{ae}$ = 97 Hz.

Free energies of activation (either $\Delta G^{\ddagger}_{e\rightarrow ts}$ or $\Delta G^{\ddagger}_{a\rightarrow ts}$) increase along both series of chlorine (1→2→3) and bromine (5→6→7) compounds as shown in **Table 2**. The substituent on the inverting nitrogen atom has to eclipse the *vicinal* equatorial alkyl group(s) in the transition state - "passing nitrogen inversion" (if the *vicinal* alkyl groups were axial we would have a " non-passing nitrogen inversion "). So, experimental values demonstrate increasing destabilization of transition states within each series. Interestingly, for the compounds whose rings are unsubstituted by alkyl groups, 1 and 5 , the lower electronegativty of bromine leads to smaller half barriers for 5 as compared with those for 1. However, bromine compounds 6 and 7 have similar barriers to chlorine compounds 2 and 3, respectively, despite the order of electronegativities of the nitrogen substituents. These facts demonstrate that the effect of larger electronegativity of chlorine is somewhat compensated by the effect of larger size of bromine.

In compound 4, relative to its 2-methyl analogues 2 and 6, the equatorial 2-ethyl group has two not very substantial effects: it shifts the equilibrium towards the N-chloro axial conformer and it increases both nitrogen inversion half-barriers. This small effect of the larger 2-ethyl relative to the 2-methyl can be understood if we consider that it can assume a rotamer with its methyl away from the inverting N-halo substituent. Also, the halogen substituent can relieve steric interactions by bending away from the 2-ethyl group in the transition state. This bending is not possible in compounds 3 and 7 where we have a second *vicinal* equatorial methyl group. Hence these are the compounds that exhibit the highest nitrogen inversion half-barriers (**Table 2**).

With N-methylpiperidine derivatives (7,15) it was verified that the introduction of only one equatorial methyl substituent α to the inverting nitrogen has a negligible effect of *ca.*0-0.1 kcal.mol^{-1} in either of the "passing half-barriers". Only when two such α substituents are introduced in the ring is a more significant increase of *ca.*0.5 kcal.mol^{-1} observed. On the contrary, in both the series of chlorine (1, 2, 3 and 4) and bromine (5, 6 and 7) piperidines studied this effect is more marked (**Table 3**). Electronic interactions are not expected to be much more severe in the transition states for N-halo inversion relative to N-methyl inversion and, if so, a compensation due to the relief of steric interactions must also be present. So, the greater increments in both half-barriers observed for the series of N-halopiperidine relative to N-alkylpiperidine derivatives must be mainly attributable to relative stabilization of their ground states rather than to relative destabilization of their transition states.

Table 3 Increments in half-barriers

	$\Delta\Delta G^{\#}_{e\to ts}$ (kcal.mol^{-1})	$\Delta\Delta G^{\#}_{a\to ts}$ (kcal.mol^{-1})
	1-Chloropiperidines	
1→2	1.7	1.4
2→3	1.3	1.0
2→4	0.5	0.9
3→4	-0.5	-0.6
	1-Bromopiperidines	
5→6	2.3	2.6
6→7	1.3	1.7

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