Ultrasonic Relaxation associated with Nitrogen and Ring Inversion in Some Piperidines, Piperidones, Morpholines, and Piperazines

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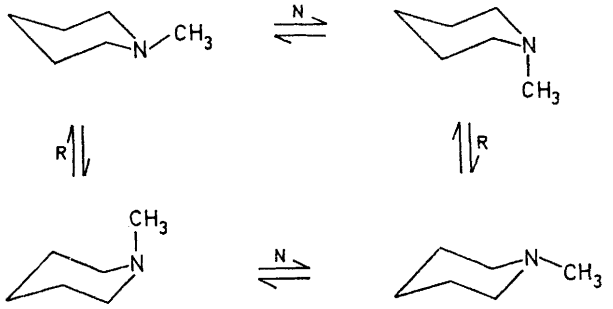
Ultrasonic relaxation arising from the perturbation of conformational equilibria involving both nitrogen and ring inversion processes have been observed in some piperidine derivatives. Conformational equilibria involving nitrogen inversion have also been investigated for some piperidones, morpholines, and piperazines. In many cases the enthalpy differences and energy barriers opposing the conformational changes in question have been found using a new method of analysis.

SATURATED six-membered nitrogen heterocycles such as piperidines, piperidones, morpholines, and piperazines are known to exist in chair conformations which may be



SCHEME 1

interconverted by two distinct processes, namely ring inversion (R) and nitrogen inversion (N), as shown for 1-methylpiperidine in Scheme 1.

Despite recent attention,[1-3] the situation concerning the roles of ring and nitrogen inversion in relation to the conformational analysis of these compounds is not clear. This is particularly true in connection with the rates at which these processes take place as well as the conformational energies of various substituents attached to the ring. For example there is a continuous debate amongst several investigators regarding the magnitude of the conformational energy of the *N*-methyl group in 1-methylpiperidine and since 1973 independent estimates ranging from 2.1 to 12.5 kJ mol^{-1} have been quoted.[4-7] As a result there is a need for more conclusive and independent experimental studies and we report here our ultrasonic absorption and relaxation measurements on several piperidines, piperidones, morpholines, and piperazines and attribute the observed relaxations to the perturbation of different types of conformational equilibria.

EXPERIMENTAL

The ultrasonic absorption and velocity measurements were taken with a pulse apparatus operating in the frequency and temperature range 25—105 MHz and 200—380 K respectively.[8] When a relaxation was observed the absorption data were displayed graphically as shown in Figure 1. The compounds used in this work are: piperidine (I), 2-methylpiperidine (II), 3-methylpiperidine (III), 4-methylpiperidine (IV), *cis*-2,6-dimethylpiperidine (V), *cis*-2,4,6-trimethylpiperidine (VI), 3,3-dimethylpiperidine (VII), 2,2,6,6-tetramethylpiperidine (VIII), 1-methylpiperidine (IX), 1,2-dimethylpiperidine (X), 1,3-dimethylpiperidine (XI), 1,4-dimethylpiperidine (XII), 1,*cis*-2,6-trimethylpiperidine (XIII), 1-*cis*-2,4,6-tetramethylpiperidine (XIV), 1,3,3-trimethylpiperidine (XV), 1,2,2,6,6-pentamethylpiperidine (XVI), 1-ethylpiperidine (XVII), 1-aminopiperidine (XVIII), 1-formylpiperidine (XIX), 1-methyl-*trans*-decahydroquinoline (XX), 1-methyl-4-piperidone (XXI), 1-

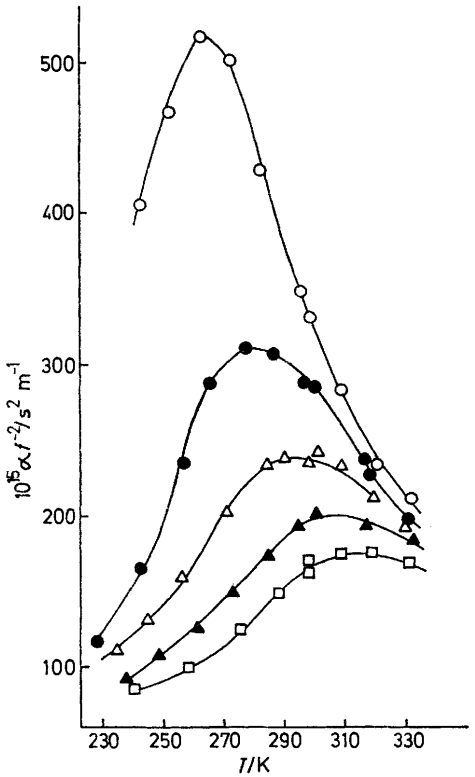


FIGURE 1 Ultrasonic relaxation spectrum for 1-ethylpiperidine: ○, *f* 25; ●, *f* 45; △, *f* 65; ▲, *f* 85; □, *f* 105 MHz

[1] J. B. Lambert. *Topics Stereochem.*, 1971, **6**, 19.
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[3] I. O. Sutherland, *Ann. Reports N.M.R. Spectroscopy*, 1971, **4**, 71.
[4] I. D. Blackburne, R. P. Duke, R. A. Y. Jones, A. R. Katritzky, and K. A. F. Record, *J.C.S. Perkin II*, 1973, 332.
[5] I. D. Blackburne, A. R. Katritzky, and T. Takeuchi, *J. Amer. Chem. Soc.*, 1974, **96**, 682.
[6] E. L. Eliel and F. W. Vierhapper, *J. Amer. Chem. Soc.*, 1974, **96**, 2257.
[7] P. J. Crowley, M. J. T. Robinson, and M. G. Ward, *J.C.S. Chem. Comm.*, 1974, 825.
[8] J. H. Andrae, R. Bass, E. L. Heasell, and J. Lamb, *Acustica*, 1958, **8**, 131.

butyl-4-piperidone (XXII), 1-benzyl-4-piperidone (XXIII), 2,6-dimethylmorpholine (XXIV), 4-methylmorpholine

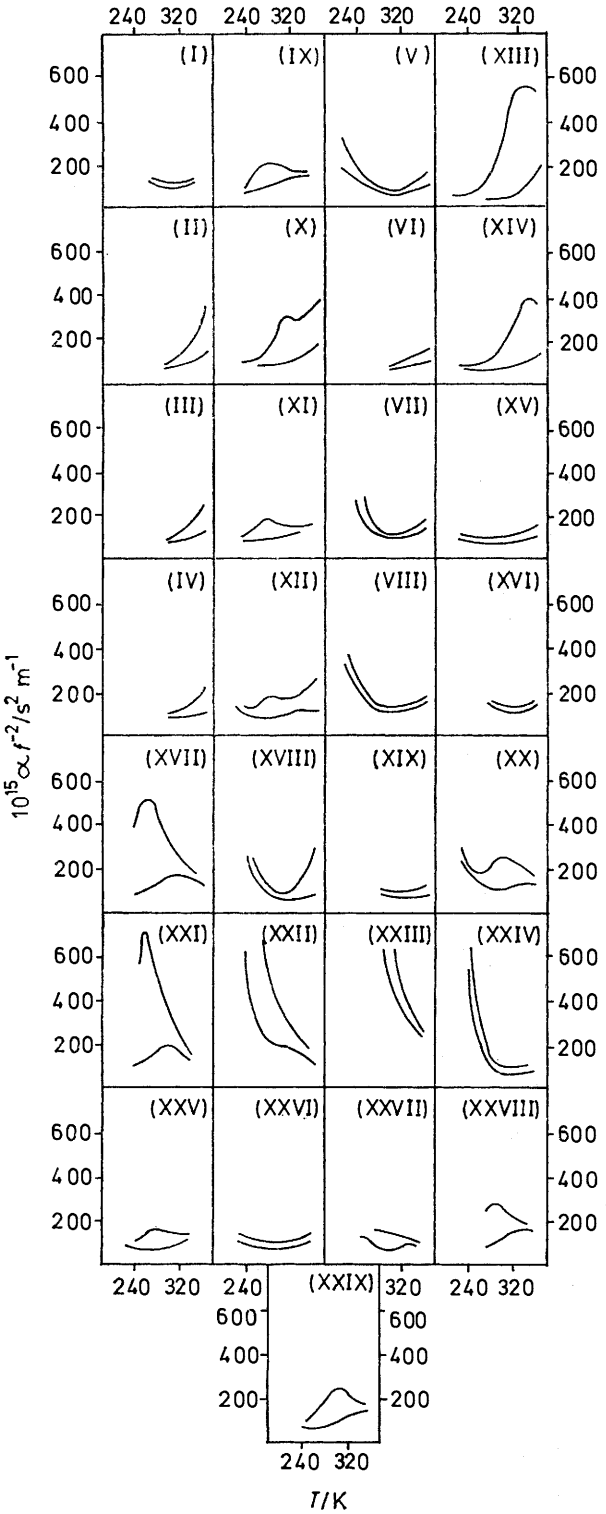


FIGURE 2 Profiles of ultrasonic spectra for some piperidines, piperidones, morpholines, and piperazines (25 and 185 MHz measurements)

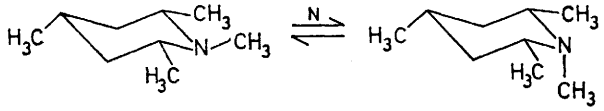
(XXV), 2,4,6-trimethylmorpholine (XXVI), 1-methylpiperazine (XXVII), 1,4-dimethylpiperazine (XXVIII), and 1,2,4-trimethylpiperazine (XXIX). Compounds (I)—(V), (VIII), (IX), (XI), (XVII)—(XIX), (XXI)—(XXV), (XXVII), and (XXVIII) were obtained from Ralph Emanuel Ltd., (VI) and (XXIX) were K and K products, and (VII) was a Fluka product. The *N*-methyl derivatives were prepared according to the method described by Clarke *et al.*[9]

The composition of all the compounds used in this work were checked by chemical analysis. All the compounds were frequently distilled at reduced pressures and were stored over molecular sieve in a desiccator. Samples of these compounds were used for measurement only once and were then redistilled and stored as described above. The configuration of compounds (V), (VI), (XIII), and (XIV) were confirmed from their n.m.r. spectra.[10,11]

RESULTS

Preliminary measurements on some of these compounds as solutes in various solvents indicated that the relaxation process was intramolecular in nature. A comparison of the strengths and temperature ranges of all the relaxation spectra is shown in the master scheme, Figure 2. Here, the profiles of the relaxation spectra are shown by plotting the α/f^2 values at 25 and 105 MHz for each compound. In some cases the full relaxation spectrum was observed in the temperature range studied (see Figure 1). When the relaxation frequencies are lower than the experimental values, the leading edge of the relaxation spectrum is observed at the higher temperatures, *e.g.* 3-methylpiperidine (III) where the α/f^2 curves at 25 and 105 MHz diverge with increasing temperature. Conversely the tail edge of the relaxation spectrum for very fast processes are as shown for 2,6-dimethylpiperidine (V) in Figure 2.

Assignment of Relaxation.—(1) *Nitrogen inversion in the N-methyl compounds.* The compounds 1,*cis*-2,6-trimethyl- and 1,*cis*-2,4,6-tetramethyl-piperidine exist almost exclusively in the chair conformation with the *C*-methyl bonds equatorial and ring inversion is completely blocked as a result of the severe *syn* axial methyl–methyl interaction that would occur in the axial conformer. In addition 1-methyl-*trans*-decahydroquinoline is known to exist in a rigid twin chair conformation.[12] The strong single relaxation process observed in these compounds is therefore associated with the perturbation of the equilibrium between the *N*-methyl-axial and -equatorial conformers arising from nitrogen inversion as shown for (XIV) in Scheme 2.

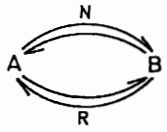


SCHEME 2

The detailed conformational mechanism involving both nitrogen and ring inversion in the *N*-substituted piperidines, morpholines, and piperidones is shown in Scheme 1 and is essentially a two state equilibrium which can be represented in equation (1). Here the nitrogen (N) and ring (R) inversion processes are shown by two distinct pathways with the

[9] H. T. Clarke, H. B. Gillespie, and S. Z. Weisahaus, *J. Amer. Chem. Soc.*, 1933, **55**, 4571.
[10] H. Booth, *Progr. N.M.R. Spectroscopy*, 1969, **5**, 149.
[11] H. Booth, J. H. Little, and J. Feeney, *Tetrahedron*, 1968, **24**, 279.
[12] H. Booth and A. H. Bostock, *J.C.S. Perkin II*, 1972, 615.

k_N and k_R values being the respective rate constants. Equilibrium (1) is characterised by a *single* relaxation time,



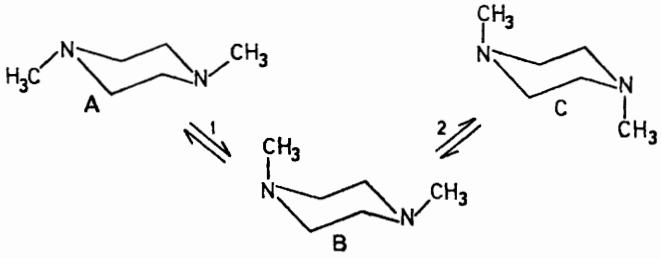
(1)

τ, given by equation (2). Thus if both nitrogen and ring inversion take place with approximately similar rates the

$$\tau = (k_R + k_{-R} + k_N + k_{-N})^{-1} \quad (2)$$

measured relaxation time is a function of all the rate constants in equation (2). On the other hand if one of these processes is much faster than the other the observed relaxation is associated with the faster process. The evidence in the following section concerning 2-, 3-, and 4-methylpiperidines and their 1-methyl derivatives as well as dynamic n.m.r. data [13-17] show that nitrogen inversion in these molecules is a much faster process than ring inversion. On this basis the origin of the relaxation found in (IX), (XVII), and (XVIII) is associated with nitrogen inversion. In ultrasonic studies the relaxation spectra which owe their origin to the same molecular process occur at similar temperatures when measured in the same frequency range. The position of the ultrasonic relaxation spectra for the *N*-methylpiperidones, -morpholines, and -piperazines are also very close to the piperidines (XIII), (XIV), (XX), (IX), and (XVII) indicating that conformational equilibria involving nitrogen inversion are being perturbed by the sound wave. In fact for (IX), (XVII), (XX), (XXI), (XXV), and (XXVII) these spectra are expected to be close because the particular segment of these molecules where nitrogen inversion takes place have identical structures. This relaxation is also present in (X), (XI), and (XII).

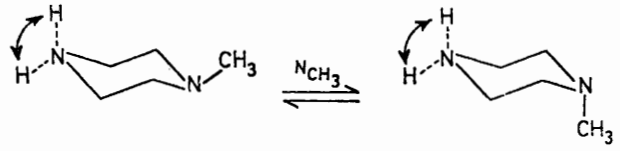
In 1,4-dimethylpiperazine the conformational mechanism associated with the ultrasonic relaxation is shown in Scheme 3 and is characterised by two relaxation times. Experimentally a single relaxation was observed for this compound and when this occurs the ultrasonic data either measures the average properties of the mechanism or one step is much faster than the other.[18]



SCHEME 3

In 1-methylpiperazine the conformational equilibrium being perturbed by the sound wave is shown in Scheme 4. During the life-time of each of the above conformers nitrogen inversion at N(4) takes place several times.

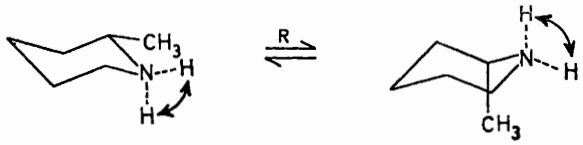
(2) *Ring inversion.* A high temperature relaxation was observed in 2-, 3-, and 4-methylpiperidine but not in piperidine itself. This relaxation owes its origin to the methyl substituents and must be associated with the perturbation of the equilibrium shown in Scheme 5 arising from ring inversion. The position of these relaxation spectra in relation to those arising from nitrogen inversion indicate that ring inversion is a much slower process. Thus during the life-time of each of the axial and equatorial isomers shown above, nitrogen inversion must take place several times. In addition to a relaxation associated with nitrogen inversion the high temperature ring inversion relaxations were also



SCHEME 4

observed for the 1,2-, 1,3-, and 1,4-dimethylpiperidines. Unfortunately the absorption data could not be analysed because, in each case, the relaxations were too close.

(3) *Other relaxation processes.* Relaxation of very small amplitudes have also been observed at the higher temperature in 2,6-dimethyl-, 2,4,6-trimethyl-, 3,3-dimethyl-, 1,3,3-trimethyl-, and 1-formyl-piperidine. The most likely origin



SCHEME 5

of the relaxations is the perturbation of conformational equilibria between the stable chair form and a high energy conformer which could be either a twist boat or a chair form with *syn*-axial methyl substituents.

The low temperature relaxation observed in *cis*-2,6-dimethylpiperidine is obviously associated with a fast process and the most likely mechanism is nitrogen inversion. Unfortunately crystallization problems prevented further investigations of other molecules with NH bonds.

Evaluation of Conformational Energies.—The enthalpy barriers $\Delta H^{\ddagger}_{21}$ opposing the less stable to more stable conformational change were evaluated from the slopes of the Eyring rate plots, log $(T\tau)^{-1}$ against T^{-1} and are listed in the Table. The relaxation time, τ, was found at several temperatures, T, by analysing the ultrasonic relaxation data for a single relaxation in the usual way.[19] In addition both the energy barriers E and enthalpy difference between the stable conformers have been evaluated using a new method of analysis employing a curve fitting procedure that has been recently developed and used successfully for several molecules in this laboratory.[20]

For a two state conformational change it was shown that

[13] R. K. Harris and R. A. Spragg, *J. Chem. Soc.* (*B*), 1968, 684.
[14] J. B. Lambert, R. G. Keske, R. E. Cahart, and A. P. Jovanavitch, *J. Amer. Chem. Soc.*, 1967, **89**, 3761.
[15] J. B. Lambert, D. S. Bailey, and B. F. Michel, *J. Amer. Chem. Soc.*, 1972, **94**, 3812.
[16] G. A. Yousof and J. D. Roberts, *J. Amer. Chem. Soc.*, 1968, **90**, 6428.
[17] R. G. Lett, L. Petrakis, A. F. Ellis, and R. K. Jensen, *J. Phys. Chem.*, 1970, **74**, 2816.
[18] J. Rassing and E. Wyn-Jones, *Adv. Mol. Relaxation Processes*, 1972, **2**, 227.
[19] J. Lamb in 'Physical Acoustics,' ed. W. P. Mason, Academic Press, New York, 1965, vol. 11a, p. 203.
[20] P. J. Heywood, J. E. Rassing, and E. Wyn-Jones, *Adv. Mol. Relaxation Processes*, 1975, **6**, 255.

when relaxation occurs the frequency and temperature dependence of the ultrasonic absorption α and velocity u are related to the conformational energies through equation (3)

$$\alpha/f^2 = \frac{P_1(P_2)^{T_0/T}}{uT^2\,[P_4(P_3)^{T_0/T} + 4\pi^2 f^2] + B} \qquad (3)$$

where P_1 and P_4 are constants, $P_2 = \exp[-\Delta H^0 + E)/RT_0]$, $P_3 = \exp(-E/RT_0)$, and B represents contributions to α/f^2 that are not related to the relaxation process in question and T_0 is a fixed temperature chosen to be 298 K. B is obtained at each temperature by extrapolating the α/f^2 values to high frequency. The constants P_1—P_4 are derived from the experimental data and equation (3) by means of a computer program incorporating a least mean square minimization procedure. The use of this method of analysis is facilitated by having reasonable initial estimates of the parameters P_1—P_4. P_3 can be estimated from the value of $\Delta H^{\ddagger}_{21}$ found using the Eyring rate plot (note that $E = \Delta H^{\ddagger}_{21} + RT$). In the N-methylpiperidines several different values for the conformational free energy of the methyl group ranging from 2.1 to 12 kJ mol^{-1} have been quoted. For the isomerization shown it is reasonable to assume that $\Delta S^0 = 0$, thus $\Delta G^0 = \Delta H^0$. Several ΔH^0 values in the above range were used to estimate P_4. Once P_3 and P_4 are chosen estimates for P_1 and P_2 are then obtained by calculation.

The values of the conformational energies found using the method are also in the Table. The consistency of the analysis was always checked by comparing the shape of the calculated ultrasonic relaxation spectrum with the experimental points as shown in Figure 1. In addition the relaxation frequency was calculated at several temperatures using equation (3) and compared with those found by analysing the ultrasonic data for a single relaxation. In all cases the agreement was satisfactory.

It is very difficult to comment on the accuracy of the conformational energies quoted in the Table. However it is possible to use the computer program in such a way that different combinations of the parameters can be varied or kept constant respectively. In this exercise we took differences between calculated and observed values of α/f^2 and f_c of up to $\pm 15\%$ as a criterion for consistency. Under these circumstances it is possible to estimate limits for ΔH^0 and E respectively. For an ultrasonic relaxation spectrum measured at frequencies of 25, 45, 65, 85, and 105 MHz over a temperature range 80 K the limits of ΔH^0 and E are of the order ± 40 and $\pm 10\%$ respectively. If the temperature range is smaller, say 40 K then the corresponding limits are *ca.* 60 and 15% respectively. It is worth noting however that the computer minimization criterion for the data in the Table is far superior to those found in estimating the above limits.

Conformational energies (in kJ mol^{-1}) associated with nitrogen (N) and ring (R) inversion in some saturated heterocycles

Molecule	Type of inversion	$\Delta H^{\ddagger}_{21}$ † Eyring plot	Analysis using equation (3)		
			ΔH^0 †	E †	$\Delta H^{\ddagger}_{21}(= E - RT)$ †
1-Methylpiperidine	N	21	3.7	25.3	24.1
1,2,6-Trimethylpiperidine	N	27	2.9	29.4	28.2
1,2,4,6-Tetramethylpiperidine	N	21	4.2	26.2	24.8
1-Methyl-*trans*-decahydroquinoline	N	18	2.2	20.8	19.6
1-Ethylpiperidine	N	20	3.5	21.0	20.0
1-Aminopiperidine	?		~16	~24	~23
1-Methylpiperidone	N	18	3.7	22.4	21.1
1-n-Butylpiperidone	N	20	3.7	22.4	21.1
4-Methylmorpholine	N	21	4.6	24.3	23.1
1-Methylpiperazine	N	20	4.6	21.6	20.3
1,4-Dimethylpiperazine	N	14	1.3	20.4	19
1,2,4-Trimethylpiperazine	N	15	3.2	18.2	16.9
2,6-Dimethylpiperidine	N	26	1.7 *	23.5	22.4
2-Methylpiperidine	R		7.1 *	42.5	41.4
3-Methylpiperidine	R		7.1 *	37.1	35.7
4-Methylpiperidine	R		7.1 *	43.3	41.9

* Assumed value. † In kJ mol^{-1}.

DISCUSSION

As a result of structural similarities especially in the vicinity of the nitrogen atom the enthalpy differences for the N-methyl compounds undergoing nitrogen inversion are expected to be close. Although a spread of values in the range 2.9 ± 1.6 kJ mol^{-1} was found experimentally, the majority are close to *ca.* 2.9 kJ mol^{-1} more in agreement with Katritzky and his collaborators [4,5] than the most recent values of Eliel and Vierhapper [6] and Robinson *et al.*[7] Under no circumstances was it possible to make the present data compatible with ΔH^0 values of the order 7.0 kJ mol^{-1} or greater. Indeed, in our experience, much weaker relaxation strengths than those observed in the present are encountered with ΔH^0 values of this magnitude. In comparing conformational energies found using different methods it should be pointed out that the present measurements were carried out on pure liquid samples and that we are quoting ΔH^0 rather than ΔG^0 values. However, for the equilibria in question ΔS^0 is expected to be very small [21] (*ca.* 0) and thus $\Delta H^0 \simeq \Delta G^0$.

The pyramidal inversion of nitrogen involves the passage through a semi planar transition state in which the lone pair possesses pure p character and the nitrogen atom is sp^2 hybridised. Most of the energy barriers opposing nitrogen inversion for the N-methyl and N-alkyl compounds discussed above are very close, *ca.* 23 kJ mol^{-1}, as would be expected. The notable exceptions are first 1,2,6-trimethyl- and 1,2,4,6-tetramethyl-piperidines, where higher energy barriers of 29 and 26 kJ mol^{-1} were found. This can be accounted for in terms of additional

[21] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, Conformational Analysis,' Interscience, New York, 1964.

non-bonded steric interactions between the α- and *N*-methyls which appears to affect the semiplanar transition state to a greater extent than the stable chair forms. In the 1,2,2,4,4-pentamethyl derivative these interactions affect all the conformations to such an extent that no relaxation was observed.

Secondly, in 1,4-dimethyl- and 1,2,4-trimethyl-piperazines it appears that the ultrasonic experiment monitors the kinetics of step 2 in Scheme 3 for the following reason. Consider the activation energies of steps 1 and 2 of this scheme by comparing respectively, the relative energies of the semi-planar transition state 1 with conformer B and also that of transition state 2 with conformer C. In transition state 2 the axial C–H bonds at C(2) and C(6) will diverge away from the axial methyl at C(4) due to the planar nitrogen atom. This results in the energy of this transition state being stabilized with respect to that of chair form C. As this interaction is absent in step 1 the activation energy for step 2 is expected to be less than step 1, which in turn should be close to those found for the *N*-methyl compounds, *i.e.* 23 kJ mol^{-1}. Analysis of the relaxation data for (XVIII) and (XXIX) gives lower barriers of 18 and 20 kJ mol^{-1} respectively which indicates that in both molecules the ultrasonic experiment measures the fastest step 2.

The present barriers opposing nitrogen inversion in the *N*-methyl compounds are lower than those derived indirectly from n.m.r. experiments.[1,2] In addition the free energy barrier, *ca.* 25 kJ mol^{-1} (at 298 K), for 1-methylpiperidone is much lower than the 35 kJ mol^{-1} (at 179 K) obtained using dynamic n.m.r.[22] This discrepancy can be explained if we assume that, as in the piperidines, morpholines, and piperazines,[13-17] the dynamic n.m.r. experiment monitors the slower process ring inversion and not nitrogen inversion as originally claimed.[22]

A low temperature relaxation attributed to the perturbation of the axial–equatorial nitrogen inversion of the N–H bond was observed in 2,6-dimethylpiperidine. Unfortunately we were unable to carry out a full analysis of the data as only the tail end of the relaxation was observed. In piperidine ΔH^0 for N–H is now thought to be well known [23] (*i.e. ca.* 1.7 kJ mol^{-1}) and by using this value in equation (3) the analysis of the data is simplified to the extent that only three disposable parameters are now required. This results in an axial–equatorial energy barrier of 23.4 kJ mol^{-1}. By analogy with the corresponding *N*-methyl compounds one expects the nitrogen inversion barrier for piperidine to be slightly lower.

[22] J. M. Lehn and J. Wagner, *Chem. Comm.*, 1970, 414.
[23] R. A. Y. Jones, A. R. Katritzky, A. C. Richards, R. J. Wyatt, R. J. Bishop, and L. E. Sutton, *J. Chem. Soc.* (*B*), 1970, 127.

We were also unable to carry out a full analysis of the relaxation associated with ring inversion in 2-, 3-, and 4-methylpiperidines because only the leading edges of the relaxations were observed at high temperatures (see Figure 2). In order to estimate the energy barrier opposing ring inversion we can simplify the analysis of equation (3) so that only three unknowns are required by assuming that ΔH^0 for the 4-methyl compound is the same as in methylcyclohexane, *i.e.* 7.2 kJ mol^{-1}. This leads to an energy barrier of 42 kJ mol^{-1} which is very close to the values found from n.m.r. data.[13-17] If it is assumed that ΔH^0 is of the same order of magnitude for the 2- and 3-methyl derivatives the corresponding energy barrier are 41 and 36 kJ mol^{-1}. In 1-aminopiperidine the leading edge of a strong relaxation process was observed at high temperatures. Preliminary analysis of the data gave the following conformational energies: ΔH^0 *ca.* 16 kJ mol^{-1} and *E ca.* 24 kJ mol^{-1}. The conformational mechanism is as in Scheme 1 and at present, we cannot ascertain whether the ultrasonic experiment measures the faster process or that the rate constants of nitrogen and ring inversion are very close. It is quite likely that a small amount of non chair conformation will be present in the molecules 2,6-dimethyl-, 2,4,6-trimethyl-, 3,3-dimethyl-, and 1,3,3-trimethyl-piperidines for the following reasons. It is well known, for example, that in 1,3-dioxans the strain involved when two methyl groups are in a *syn*-axial position is so large that some of the molecules are forced into a twist conformation.[24] In addition an ultrasonic relaxation [25] arising from the perturbation of an equilibrium involving chair and twist boat conformers has been observed in some *gem*-dimethyl derivatives of 1,3-dioxan. On the basis of this evidence we conclude that in (V)—(VII) and (XV) steric interaction in the axial chair form will cause the ring to distort to such an extent that a small fraction of the molecules exist in a twist conformation and the observed weak relaxation results from the perturbation of the equilibrium between this twist conformation and the stable chair form of the molecule. Unfortunately the amplitude parameters associated with these high temperature relaxations were much too weak to carry out meaningful analyses.

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[25] G. Eccleston and E. Wyn-Jones, *J. Chem. Soc.* (*B*), 1971, 2469.