Tetrahedron Letters,Vol.26,No.37,pp 4533-4536,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

# BARRIERS TO INVERSION AT NITROGEN IN BICYCLIC AMINES AND HYDRAZINES

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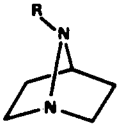
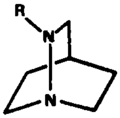
Summary: Nitrogen inversion barriers have been measured for 7-chloro-1,7-diazabicyclo-[2.2.1] heptane and [2.2.2]octane; the unusual nature of the bridging nitrogen in bicyclo [2.2.1] systems is discussed.

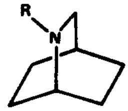
The effects of ring strain and heteroatom substitution in raising the barrier to inversion are well known.[1] We have been interested in the inversion process at nitrogen in strained azabicycles[2] and, in particular, in derivatives of the 7-azabicyclo[2.2.1]heptane skeleton. In this latter system, the conformational stability at nitrogen has been sufficient to allow study of the stereochemical implications of reactions at nitrogen.[3] We have also studied the diazabicycles (1) in order to assess the combined influence of the so-called 'bicyclic effect'[1] and the presence of an additional adjacent nitrogen on both the stereochemical integrity at nitrogen and on the chemistry of (1). The homologue (2) was included for comparison purposes.



**(1a)** R = Cl
**(1b)** R = H
**(1c)** R = Me

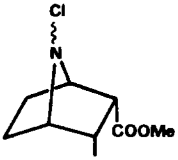


**(2a)** R = Cl
**(2b)** R = H
**(2c)** R = Me



**(3a)** R = Cl

**(3c)** R = Me



**(4)**

A recent paper[4a] concerning N-chlorohydrazines [including (1a) as well as acyclic systems] prompts us to add our quantitative measurements to the discussion. We report also the measurement of $\Delta G^{\ddagger}_{inv}$ for (1b) which is, as far as we are aware, the first such measurement by VT NMR at secondary nitrogen in an azabicycle.

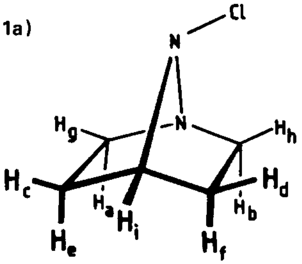
The 300 MHz $^{1}$H NMR spectrum of (1a)[5a] at ambient temperature is shown in Fig. 1. A full analysis was performed with the aid of a 2-D COSY spectrum and the results are summarised in Table 1. Protons $H_g$ and $H_h$ were well separated at 300 MHz, as were the signals due to $H_c$ and $H_d$ but VT studies were performed at 100 MHz in order to lower the coalescence temperature as far as possible whilst maintaining reasonable peak separation. Signals due to $H_g$ and $H_h$ coalesced at 167 °C in chlorobenzene in a sealed nmr tube; $H_c$ and $H_d$ behaved similarly. A small amount of dark oily material separated from solution, but the spectrum was essentially unchanged on recooling the sample.[4b] The remarkable stability of (1a) is a result of 'Bredt's rule protection' and is in sharp contrast to the extreme instability of (2a) which began to decompose above -20°C. The N-chlorohydrazine (2a) was therefore prepared and handled at low temperature.[5b] Coalescence of the signals due to the protons on C-3 at δ3.85 and 3.15 occurred at -25°C. On warming to room temperature, (2a) decomposed and an intractable gum separated from solution.

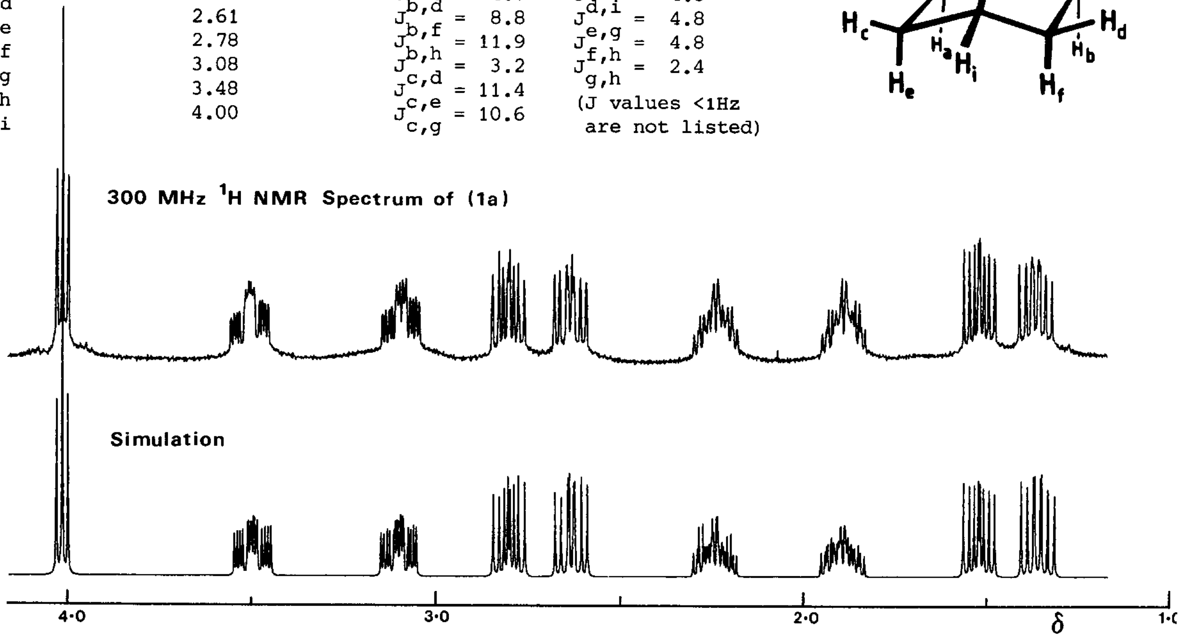
The secondary amine (1b) in $CFCl_3/CH_2Cl_2/CD_2Cl_2$ solution showed singlets at δ32.1(C-3, C-5) 55.9(C-2, C-6) and 57.3(C-4) in the $^1H$-decoupled $^{13}C$ spectrum even at -90°C. However, on further cooling, the signal at δ55.9 broadened and split into two signals at -140°C.

TABLE 1

| PROTON | CHEMICAL SHIFT (δ) | COUPLING CONSTANTS (Hz) | |
|---|---|---|---|
| $H_a$ | 1.34 | $J_{a,c}$ = 5.2 | $J_{c,i}$ = 4.7 |
| $H_b$ | 1.50 | $J_{a,e}$ = 10.3 | $J_{d,f}$ = 11.9 |
| $H_c$ | 1.87 | $J_{a,g}$ = 11.4 | $J_{d,h}$ = 11.1 |
| $H_d$ | 2.22 | $J_{b,d}$ = 4.7 | $J_{d,i}$ = 4.8 |
| $H_e$ | 2.61 | $J_{b,f}$ = 8.8 | $J_{e,g}$ = 4.8 |
| $H_f$ | 2.78 | $J_{b,h}$ = 11.9 | $J_{f,h}$ = 4.8 |
| $H_g$ | 3.08 | $J_{c,d}$ = 3.2 | $J_{g,h}$ = 2.4 |
| $H_h$ | 3.48 | $J_{c,e}$ = 11.4 | (J values <1Hz are not listed) |
| $H_i$ | 4.00 | $J_{c,g}$ = 10.6 | |

(1a)





The coalescence data and $\Delta G^{\ddagger}$ values are summarised in Table 2.[6] The high barrier to inversion at nitrogen in (1a) [$\Delta G^{\ddagger}_{440K}$ = 22.0 kcal $\text{mol}^{-1}$] and in many other 7-azabicyclo[2.2.1]heptane derivatives [$\Delta G^{\ddagger}$ = *ca*. 19-25 kcal $\text{mol}^{-1}$] is of interest and deserves comment. Shustov *et al* rationalised the high configurational stability at nitrogen in terms of two main factors: (a) the inclusion of N-7 in a strained bridge, and (b) the presence of Cl and N ligands on N-7.

We believe that point (a) should not be over-emphasised.[7] Thus the CNC bond angle in 7-azabicyclo[2.2.1]heptyl derivatives[8a] is greater than that in N-chloroazetidine for which $\Delta G^{\ddagger}_{235K}$ is *ca*. 13.4 kcal $\text{mol}^{-1}$.[8b] When comparison is made with (4) [$\Delta G^{\ddagger}_{413K}$ = 21 kcal $\text{mol}^{-1}$ [1]] the difference is seen to be 7.6 kcal $\text{mol}^{-1}$ and this cannot reasonably be ascribed to bond angle strain. Similarity between the $\Delta G^{\ddagger}$ values for (1a) and (4), discussed below, give no cause to view the hydrazine in a different light to the amine.

Table 2 Coalescence Data

| Compound | NMR Nucleus (frequency) | Solvent | Coalescence Temp. $T_c$ (°K) | $\Delta\nu$ (Hz) | $\Delta G^{\ddagger}$ at $T_c$ (kcal $mol^{-1}$) |
|---|---|---|---|---|---|
| (1a) | $^1H$ (100 MHz) | PhCl | 440 (±5) | 51 (±3) | 22.0±0.3 |
| (2a) | $^1H$ (300 MHz) | $CDCl_3$ | 248 (±3) | 192 (±3) | 11.4±0.2 |
| (1b) | $^{13}C$ (100 MHz) | $CFCl_3$<br>$CH_2Cl_2$<br>$CD_2Cl_2$ | 153 (±3) | 249 (±3) | 6.8±0.3 |

The errors quoted are pessimistic values and are almost certainly over-estimates.

The effect of electronegative ligands (point (b)) has been explained in terms of electronegativity and lone-pair/lone-pair interactions at the transition state for inversion.[1] However, the extra nitrogen in (2a) produces an increase in $\Delta G^{\ddagger}$ of only 0.8 kcal $mol^{-1}$ over the value for (3a)[9a] of 10.6 kcal $mol^{-1}$ since the N-1 lone pair is effectively orthogonal to the N-2 lone pair (p-hybridised) at the transition state for inversion. Similar, small effects of a second nitrogen are observed in the corresponding N-methyl analogues (2c) and (3c) where the difference is ca. 1.1 kcal $mol^{-1}$.[9b] It seems reasonable to assume that the even tighter constraints on the N-N relationship in (1a) will limit the increment due to the second nitrogen to a similar, small value and this is supported by the observed difference of only 1 kcal $mol^{-1}$ between the values for (1b) and (4) [$\Delta G^{\ddagger}$ = 22 and 21 kcal $mol^{-1}$ respectively]. With regard to the effect of chlorine, substitution of an N-Cl for an N-Me substituent usually raises $\Delta G^{\ddagger}$ in the ratio Cl/Me = 1.28 in cyclic systems.[10] Where the intrinsic barrier in an amine is already high, the barrier-raising effect of Cl is clearly augmented in absolute terms but the chlorine is not the primary cause of very high barriers in the systems under discussion.[11]

In organic amines, inversion barriers above ca. 19 kcal $mol^{-1}$ are only exhibited by aziridines (where the effect is explained satisfactorily by ring strain) and by a family of derivatives of the 7-azabicyclo[2.2.1]heptyl system in which the unusual nature of the bridging nitrogen is also indicated by dramatic deshielding in the $^{15}N$ NMR.[12] We are not aware of a satisfactory explanation of these properties in these bicyclic amines.[13]

We thank Dr S.F. Nelsen for an interesting and helpful discussion, Drs O. Howarth and E. Curzon of the SERC high-field nmr service at Warwick for the VT nmr work on (1b) and Dr D.L. Turner for the 300 MHz spectrum and simulation for (1a). We thank the SERC for support.

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2. J.R. Malpass and N.J. Tweddle, J. Chem. Soc. Perkin II, 1978, 120.
3. M.L. Durrant and J.R. Malpass, J. Chem. Soc. Chem. Commun., 1981, 1028; J.R. Malpass and M.P. Walker, ibid., 1979, 585.

4a. G.V. Shustov, N.B. Tavakalyan and R.B. Kostyanovsky, Tetrahedron, 1985, 41, 575.

b. These authors record no coalescence in the $^{13}C$ nmr spectrum of (1a) at 120°C in $PhNO_2$ at which temperature the sample was observed to have decomposed completely.

5a. (1b) was prepared by modification of procedures used by others [W. Oppolzer, Tetrahedron Lett., 1972, 1707; G.V. Shustov, N. Tavakalyan and R.B. Kostyanovsky, Izv. Akad. Nauk SSSR,Ser. Khim., 1981, 1677.] Full details (including formation of dimeric by-products in the cyclisation step) will be reported in the full paper. Sodium hypochlorite was used to convert (1b) into (1a).

b. (2b) was prepared essentially by the method of S.F. Nelsen, P.M. Gannett and D.J. Steffek, J. Org. Chem., 1980, 45, 3857. Conversion into (2a) was carried out with N-chlorosuccinimide (1.2 equiv.) in $CDCl_3$ at -40°C. After stirring for 0.5h at that temperature and filtration at low temperature, the sample was transferred to the nmr probe, pre-cooled to -40°C.

6. It is assumed that the values for (1a) and (2a) are associated with inversion at nitrogen; reversible formation of a diazenium ion is most unlikely here in view of the 'Bredt's rule protection' afforded to the N-N-Cl moiety.
7. J.R. Malpass, Comprehensive Organic Chemistry, Pergamon, Oxford, 1979, Vol. 6, Ch. 1, p.28.

8a. This estimate is not just based on work with models but also on X-ray studies of N-chloro-7-azabenzonorbornene (N-chloro-1,2,3,4-tetrahydro-1,4-iminonaphthalene) derivatives [J.W. Davies, J.R. Malpass, J. Fawcett, R. Lindsay, D.R. Russell and L.J. Sherry, manuscript in preparation] which give CNC bond angles of ca. 95.7-97.3°.

b. CNC bond angles have been reported for N-chloroazetidine ['about 90°'; J.B. Lambert, W.L. Oliver Jr. and B.S. Packard, J. Amer. Chem. Soc., 1971, 93, 933] and azetidine [91.2°; G. Pfafferott, H. Oberhammer, J.E. Boggs and W. Caminati, ibid., 1985, 107, 2305].

9a. S.F. Nelsen and P.M. Gannett, J. Amer. Chem. Soc., 1982, 104, 5292.

b. S.F. Nelsen and G.R. Weisman, ibid., 1976, 98, 1842.

10. H. Kessler and D. Leibfritz, Tetrahedron Letters, 1970, 4289. n.b. the $\Delta G^{\ddagger}$ ratio for (2a)/(2c) is higher than this. We are investigating the ratio for (1a)/(1c).
11. It is noteworthy that a high barrier (19.5 kcal $mol^{-1}$) has been reported for an N-methylazabicyclo[2.2.1]heptadiene derivative [J.M. Lehn, Ref. 1. (above), compound 138a] but see also data for N-benzyl compounds, W.J. Deloughry and I.O. Sutherland, J. Chem. Soc. Chem. Commun., 1971, 1104.
12. J.W. Davies and J.R. Malpass, accompanying paper.
13. Attempts are presently underway to shed light on this problem using theoretical methods, T.A. Claxton, University of Leicester.

(Received in UK 1 July 1985)