Measurement of Nitrogen Inversion Barriers and Invertomer Ratios in Constrained Azabicyclic Systems

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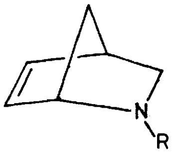
Both possible nitrogen invertomers of the *N*-chloro-derivatives of 2-azabicyclo[2.2.1]hept-5-ene (1b) and its 3,3-dideuterio-derivative (5), 2-azabicyclo[2.2.1]heptane (2b), and 2-azabicyclo[2.2.2]oct-5-ene have been observed directly at low temperatures using ^{1}H n.m.r., the signals due to the minor invertomers being identified with the aid of homonuclear INDOR spectroscopy. Inversion barriers increase as the size of the carbon bridges is decreased, reaching *ca.* 14.8 kcal mol^{-1} in the case of *endo*- → *exo*- (1b). *exo* : *endo* Invertomer ratios in these and other azabicyclic systems are discussed.

EXTENSIVE study of nitrogen inversion in monocyclic systems has long established that the barrier to inversion generally increases as ring size decreases.[1] In strained azamonocycles, nitrogen inversion may be studied without complications from ring inversion (which may intrude in the larger monocycles) or from hindered bond rotation (which may cause difficulty in acyclic amines). On this basis, Lehn and Wagner [2] extended the study by introducing an extra two-carbon bridge across six- and seven-membered rings {to give 3-azabicyclo[3.2.2]nonanes and 2-azabicyclo[2.2.2]octanes (4) in which nitrogen inversion was the only temperature-dependent process} and observed a further increase in the energy barriers. Measurements in 7-azabicyclo[2.2.1]heptyl systems had already shown [1a,3] that the barriers present in azabicycles may be much higher than those expected simply on the basis of angle strain (a phenomenon referred to as the ' bicyclic effect ' [1a]).

The ready availability of 2-azabicyclo-[2.2.1]hept-5-enes (1), -[2.2.1]heptanes (2), and -[2.2.2]oct-5-enes (3) from other work [4] prompted an investigation into the effect of progressively tighter constraints imposed in moving back along the series from 2-azabicyclo[2.2.2]octanes (4) to (1) from two points of view. First, to measure the anticipated ' bicyclic effect ' and the extent of the resulting increase in the nitrogen inversion barriers. Secondly, to measure the relative populations of the two isomers in systems (1)—(3) [which, unlike (4), do not possess a plane of symmetry] bearing in mind steric constraints in each case and also possible homoallylic interaction between the nitrogen lone pair and the 5,6-double bond in (1) and (3).

The *N*-chloro-derivatives (1b)—(3b) were selected for study as the most appropriate for comparison with results in other systems.[1a] Further, the expected increase in the inversion barrier due to the introduction of chlorine at the nitrogen atom [1] was expected to facilitate observation of the inversion phenomenon using variable-temperature ^{1}H n.m.r. spectroscopy. With the aid of homonuclear INDOR spectroscopy at low temperatures, signals characteristic of both invertomers have been identified in each case and analysis of the spectra has provided quantitative estimates of invertomer ratios and inversion barriers in (1b)—(3b). Studies of derivatives of (3) and (4) have been published recently by two groups. Morishima and Yoshikawa have used ^{1}H and ^{13}C n.m.r. contact shift experiments at ambient temperature to establish qualitative *exo* : *endo* preferences for (3a and c) and also performed CNDO/2 MO calculations.[5] In a ^{13}C study of bicyclo[2.2.2]octyl-hydrazines and -amines, Nelsen and Weisman have reassessed Lehn and Wagners' results concerning the inversion barriers in (4c) and its 1-



(1)

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b; R = Cl
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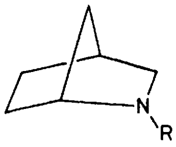

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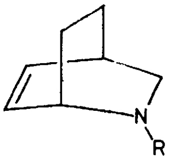

(3)

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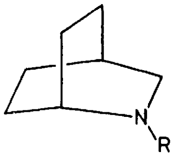

(4)

a; R = H
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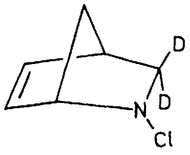
c; R = CH_3
d; R = CD_3



(5)

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[1] (*a*) J. M. Lehn, *Fortschr. Chem. Forsch.*, 1971, **15**, 311; (*b*) H. Kessler, *Angew. Chem. Internat. Edn.*, 1970, **9**, 219; (*c*) A. Rauk, L. C. Allen, and K. Mislow, *ibid.*, p. 400.

[2] J. M. Lehn and J. Wagner, *Chem. Comm.*, 1970, 414.

[3] (*a*) R. Kitzing, R. Fuchs, M. Joyeux, and H. Prinzbach, *Helv. Chim. Acta*, 1968, **51**, 888; (*b*) V. Rautenstrauch, *Chem. Comm.*, 1969, 1122.

[4] J. R. Malpass and N. J. Tweddle, *J.C.S. Perkin I*, 1977, 874.

[5] I. Morishima and K. Yoshikawa, *J. Amer. Chem. Soc.*, 1975, **97**, 2950.

methyl derivative and have recorded the temperature-independent spectrum of (3c).[6]

RESULTS

The parent amines (1a)—(3a) were converted to the *N*-chloro-derivatives (1b)—(3b) in $CFCl_3$ by a modification of the method of Graefe using sodium hypochlorite.[7] The specifically deuteriated compound (5) was prepared from 2-azabicyclo[2.2.1]hept-5-en-3-one[4] by reduction with $LiAlD_4$ followed by hypochlorite treatment.

The n.m.r. spectra of (1b)—(3b) and (5) at 30 °C were consistent with those expected under conditions where inversion was rapid on the n.m.r. time scale and each proton gave only one signal whose position was the population-weighted mean of the positions of the signals due to the protons in the separate invertomers.

TABLE 1

Selected n.m.r. data for the invertomers of the *N*-chloroamines (1b)—(3b) in $CFCl_3$

	(1b)		(2b)		(3b)	
Temperature (°C)	−54		−87		−84	
Invertomer	Major	Minor	Major	Minor	Major	Minor
Cl	*endo*	*exo*	*exo*	*endo*	*endo*	*exo*
			Chemical shifts (δ)			
H(3-*exo*)	3.64	*ca.* 3.1	2.98	3.41	3.49	2.76
H(3-*endo*)	2.04	*ca.* 3.1	3.20	2.37	2.50	3.22
H(4)	*ca.* 3.1	*ca.* 3.1	2.43	*ca.* 2.3		
H(7-*anti*)	1.58	1.80	1.37			
H(7-*syn*)	1.58	2.22	2.05			
			Coupling constants (Hz)			
J(3-*exo*,3-*endo*)	11		12	11 ± 1	11	11
J(3-*exo*,4)	3		4	3		
J(7-*syn*,7-*anti*)		9	10			

The signals due to the bridgehead methine protons H(1) (adjacent to nitrogen) and H(4) were assigned on the basis of their chemical shifts. In each case, the signals due to the geminal pair H(3-*exo*) and H(3-*endo*) appeared as the two halves of a widely-spaced AB system with a typical coupling constant of 10—12 Hz. The *exo–endo* signals were distinguished on the basis of vicinal and/or long-range coupling to other protons. Thus in (1b) and (2b), H(3-*exo*) coupled to H(4) (*J* 3—4 Hz) and H(3-*endo*) was broadened due to ω-coupling to H(7-*anti*). In (3b), H(3-*exo*) coupled to H(4) (*J* 2 Hz) and each part of the H(3-*endo*) doublet appeared as a triplet (*J* *ca.* 2.5 Hz) due to approximately equal vicinal coupling ($J_{3\text{-}endo.\ 4}$) and ω-coupling ($J_{3\text{-}endo.\ 8\text{-}anti}$).

As the solutions of the *N*-chloroamines were cooled, the spectra initially broadened and then sharpened until further cooling produced no significant change. The low-temperature spectrum of each sample indicated the presence of two species which were assigned as the *exo*- and *endo*-chlorine invertomers. All variable temperature changes were reversible. The detailed changes and assignments will be discussed for each case in turn and the decisions regarding the configuration of the chlorine will then follow. Bold type is used for the major invertomer in each pair.

2-Chloro-2-azabicyclo[2.2.1]*hept-5-ene* (1b).—The n.m.r. spectrum of (1b) at −50 °C is recorded in Figure 1 and selected assignments are summarised in Table 1. The assignments of the signals due to the major invertomer follow easily from the general observations above. The analysis was confirmed by decoupling experiments at −50 °C where necessary; homonuclear INDOR experiments were essential for the analysis of closely-spaced multiplets and selected results are superimposed onto Figure 1. At first sight, the only evidence for a minor invertomer was a small doublet at δ 1.80 but this was shown to be half of an AB system; the other doublet at δ 2.20, whilst clearly visible in the INDOR experiment, was partially obscured by the signal due to **H**(3-*endo*) in the single resonance spectrum. The assignment of these high-field signals to the geminal 3-protons seemed unreasonable on chemical shift grounds. Furthermore, the coupling between these two protons (*J* 9 Hz) was smaller than the typical values of $J_{3\text{-}endo,\ 3\text{-}exo}$ in this series (*J* 11—12 Hz; Table 1) and neither of the doublets showed a line-width change consistent with the collapse of 3 Hz coupling (expected for $J_{3\text{-}exo.\ 4}$ in the minor invertomer) on conventional double irradiation of the multiplet at δ 3.1 which included H(4). This minor AB system was therefore assigned to the 7-protons.

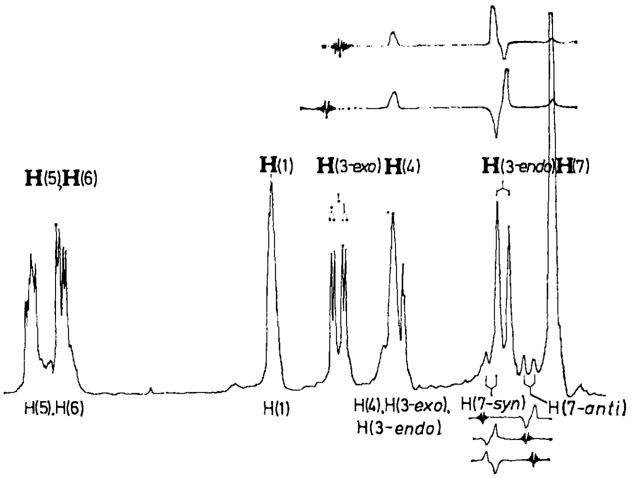

FIGURE 1 N.m.r. spectrum of 2-chloro-2-azabicyclo[2.2.1]-hept-5-ene (1b) at −50 °C in $CFCl_3$

Integration of the low-temperature spectrum revealed that the multiplet at δ 3.1 was composed of **H**(4), H(4), H(3-*exo*), and H(3-*endo*).

Complete confirmation of these assignments followed from

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[6] S. F. Nelsen and G. R. Weisman, *J. Amer. Chem. Soc.*, 1976, **98**, 1842.

[7] A. F. Graefe and R. E. Meyer, *J. Amer. Chem. Soc.*, 1958, **80**, 3939.

the variable-temperature n.m.r. analysis of the deuteriated analogue (5) in which the signals due to H(3) and **H**(3) (*exo* and *endo*) were absent (Figure 2).

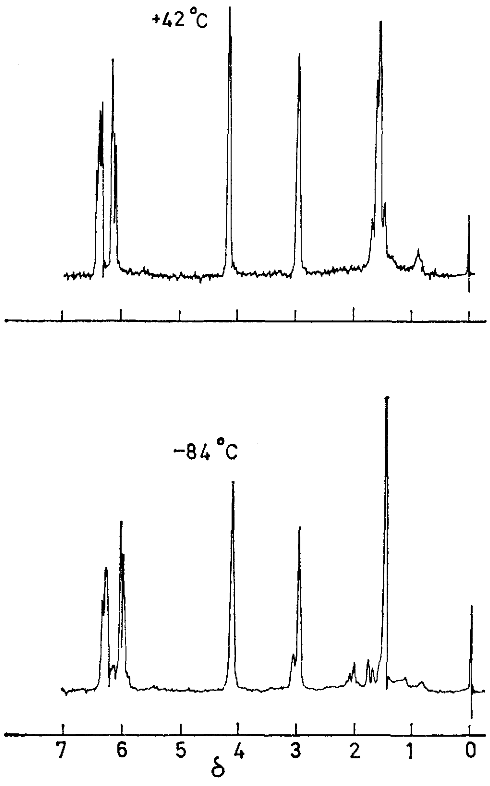


FIGURE 2 N.m.r. spectrum of 2-chloro-3,3-dideuterio-2-azabicyclo[2.2.1]hept-5-ene (5) in $CFCl_3$

2-Chloro-2-azabicyclo[2.2.1]*heptane* (2b).—The low-temperature n.m.r. spectrum (−84 °C) and selected INDOR experiments are shown in Figure 3. **H**(1) and **H**(4) were readily identified and the higher-field portion of the AB system due to **H**(3) showed the additional coupling (*J* 4 Hz) anticipated for **H**(3-*exo*). The INDOR response on monitoring the broad **H**(4) signal confirmed this significant interaction with **H**(3-*exo*) and also the lack of interaction with **H**(3-*endo*), the dihedral angle approaching 90 °C. A widely-spaced AB system, δ 2.05 and 1.37 (*J* 10 Hz), superimposed onto the complex absorption due to protons at the 5- and 6-positions was assigned to the geminal **H**(7) pair. The doublet at δ 2.05 was assigned to **H**(7-*syn*) (*syn* to the nitrogen) since it showed more fine structure due presumably to ω-coupling to **H**(5-*endo*) and **H**(6). That the sharper **H**(7) doublet at δ 1.37 corresponded to the proton *anti* to nitrogen [coupled weakly to **H**(3-*endo*)] was confirmed by the observation of small INDOR signals on monitoring the more intense of the **H**(3-*endo*) lines.

Two minor doublets in the spectrum at δ 2.37 and 3.41 were the only immediately visible features of the minor invertomer and were assigned to H(3-*endo*) and H(3-*exo*) respectively. The positions of the remaining hidden lines in this AB system were found using INDOR experiments and the geminal coupling constant was shown to be 11 ± 1 Hz. A broad signal at δ 2.30 which overlapped with H(3-*endo*) was assigned to H(4).

2-Chloro-2-azabicyclo[2.2.2]*oct-5-ene* (3b).—The low-temperature n.m.r. spectrum and selected INDOR results are shown in Figure 4. **H**(1), the **H**(3) pair, and **H**(4) were easily identified as shown.

A minor doublet at δ 3.22 was shown to be associated with a partially obscured doublet at δ 2.76 and on the basis of relative chemical shifts and the similarity of J_{geminal} (11 Hz) with that of the major invertomer, these signals were assigned to H(3-*endo*) and H(3-*exo*) respectively. The reverse assignment was inconsistent with the observed position of the population-weighted-mean signals above coalescence and the greater half-width of H(3-*endo*) compared to H(3-*exo*) signals was predictable. An INDOR response at δ 2.6 on monitoring each of the H(3-*endo*) lines was assigned to H(4) but no further analysis of the spectrum was attempted.

The observed *exo* : *endo* preferences are recorded in Table 5 and the detailed n.m.r. assignments must now be justified.

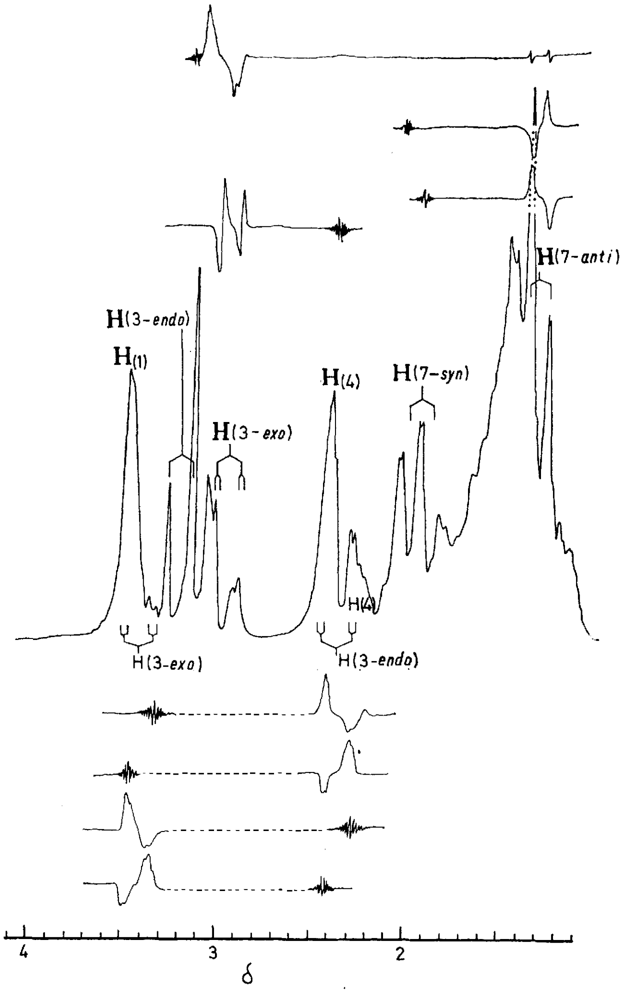


FIGURE 3 N.m.r. spectrum of 2-chloro-2-azabicyclo[2.2.1]-heptane (2b) at −84 °C in $CFCl_3$

Purely on the basis of the steric interactions experienced by *exo*- and *endo*-substituents, the following picture emerges. Replacement of a saturated two-carbon bridge in (4b) by an unsaturated two-carbon bridge [as in (3b)] would be expected to displace the equilibrium towards a major invertomer with chlorine in the *endo*-position (observed 91%). In the saturated [2.2.1] heptane system (2b), the observed

72 : 25 ratio must surely correspond to an *exo*-chlorine preference on steric grounds. On the basis of any simple argument, the replacement of the saturated bridge by an unsaturated bridge is unlikely to increase this *exo*-preference. and the 88 : 12 ratio may be assigned to *endo*- (1b) : *exo*- (1b).

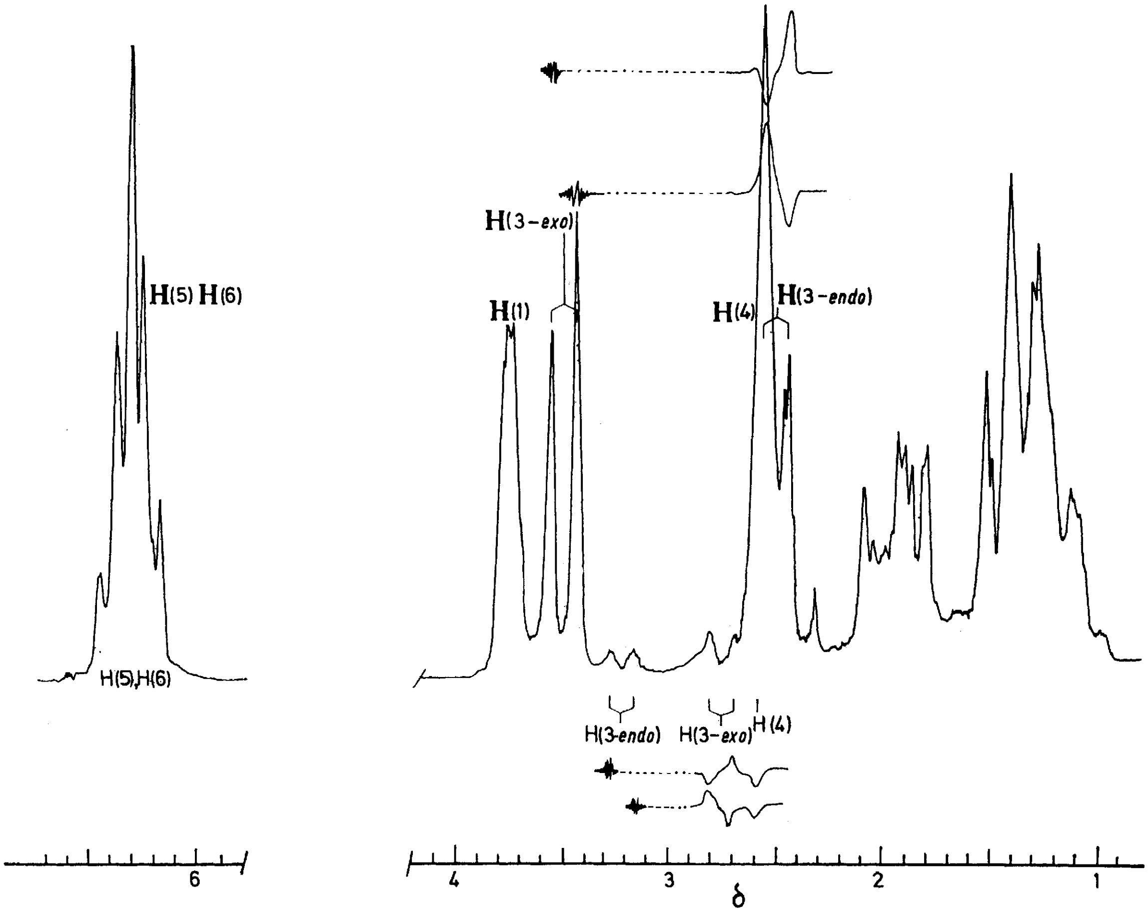


FIGURE 4 N.m.r. spectrum of 2-chloro-2-azabicyclo[2.2.2]-oct-5-ene (3b) at −87 °C in $CFCl_3$

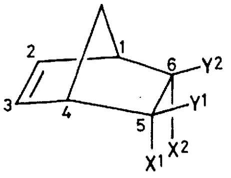
TABLE 2

Dependence of proton chemical shifts upon orientation of vicinal chlorine in selected bicyclic molecules

Compound	Proton	Chemical shift for given chlorine configuration on adjacent carbon (δ)	Chemical shift for alternative chlorine configuration (δ)	Upfield shift of proton on bringing adjacent chlorine ' into line ' (δ)	Ref.
(1b)	H(3-*exo*)	Cl(2-*endo*) 3.64	Cl(2-*exo*) 3.1	0.54	Table 1
(1b)	H(3-*endo*)	Cl(2-*exo*) 3.1	Cl(2-*endo*) 2.04	1.06	Table 1
(2b)	H(3-*exo*)	Cl(2-*endo*) 3.41	Cl(2-*exo*) 2.98	0.43	Table 1
(2b)	H(3-*endo*)	Cl(2-*exo*) 3.20	Cl(2-*endo*) 2.37	0.83	Table 1
(3b)	H(3-*exo*)	Cl(2-*endo*) 3.49	Cl(2-*exo*) 2.76	0.73	Table 1
(3b)	H(3-*endo*)	Cl(2-*exo*) 3.22	Cl(2-*endo*) 2.50	0.72	Table 1
(6a)–(6b)	H(5-*exo*)	Cl(6-*endo*) 4.50	Cl(6-*exo*) 4.18	0.32	8*b*
(6c)–(6d)	H(5-*endo*)	Cl(6-*exo*) 4.03	Cl(6-*endo*) 3.57	0.46	8*b*
(6e)–(6f)	H(5-*exo*)	Cl(6-*endo*) 4.4	Cl(6-*exo*) 4.25	0.15	8*a*, *b*
(7a)–(7b)	H(2-*exo*)	Cl(3-*endo*) 4.45	Cl(3-*exo*) 4.27	0.18	8*b*
(7c)–(7d)	H(2-*endo*)	Cl(3-*exo*) 4.17	Cl(3-*endo*) 3.68	0.49	8*b*

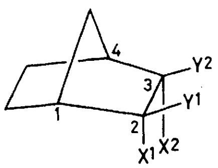
However, the *endo* : *exo* assignments for (1b) and (3b) *could* be completely reversed if steric factors were completely over-ridden by a homoallylic interaction between the π-bond and the nitrogen lone pair which substantially favoured a lone-pair orientation *endo* to the π-system (*i.e.* an attractive interaction between the *n*- and π-systems [5]). It therefore seems reasonable to use available literature comparisons as far as possible to reinforce our n.m.r. assignments and three examples of empirical correlations based on work in norbornene and norbornane systems will be considered.

First, the chemical shift of a proton at C-2 in norbornanes or C-5 in norbornenes is highly dependent on the geometry of a vicinal chlorine (at C-3 or -6 respectively).[8] It is clear that for 5,6-dihalogenonorbornenes (6) and 2,3-dihalogenonorbornanes (7) an *exo*-proton at C-5 in (6) or C-2 in (7) consistently experiences a substantial upfield shift when the chlorine on the adjacent carbon moves from an *endo* to an *exo* (in-line) position. Similarly, an *endo*-proton at C-5 in (6) or C-2 in (7) experiences a greater upfield shift when the adjacent chlorine moves from an *exo* to an *endo* (in-line) position, all other factors remaining unchanged. This provides a basis for comparison of the azabicycles (1b)—(3b) where similar upfield shifts are observed, the shifts again being greater when considering *endo*- rather than *exo*-protons at C-3 except in the case of (3b) where they are approximately equal. The magnitude of the shifts is greater in the *N*-chloro-compounds but always in the same direction. If the major–minor assignments in (1b)—(3b) are reversed, then similar arguments lead to *downfield* shifts which do not correlate satisfactorily.



(6)

a; X^1 = Br, X^2 = Cl, Y^1 = Y^2 = H
b; X^1 = Br, X^2 = Y^1 = H, Y^2 = Cl
c; X^1 = X^2 = H, Y^1 = Br, Y^2 = Cl
d; X^1 = Y^2 = H, X^2 = Cl, Y^1 = Br
e; X^1 = X^2 = Cl, Y^1 = Y^2 = H
f; X^1 = Y^2 = H, X^2 = Y^1 = Cl
g; X^1 = X^2 = Y^1 = Y^2 = H



(7)

a; X^1 = Br, X^2 = Cl, Y^1 = Y^2 = H
b; X^1 = Br, X^2 = Y^1 = H, Y^2 = Cl
c; X^1 = X^2 = H, Y^1 = Br Y^2 = Cl
d; X^1 = Y^2 = H, X^2 = Cl, Y^1 = Br
e; X^1 = X^2 = Y^1 = Y^2 = H

Secondly, hydrogenation of the 2,3-double bond in norbornenes produces a downfield shift of the *endo*-protons at C-5 and -6 and a smaller shift of the *exo*-protons at C-5 and -6 which is usually upfield,[9] although inconsistencies for *exo*-protons have been noted.[8b] This is illustrated in Table 3 using norbornene–norbornane. The same downfield *endo*-shift and smaller upfield *exo*-shift clearly emerges from comparison of (1b) and (2b) in agreement with the proposed assignments.

TABLE 3

Chemical shift differences (Δ) of protons at C-3 of 2-chloro-2-azabicyclo[2.2.1]hept-5-ene (1b) and at C-5 and -6 of bicyclo[2.2.1]hept-5-ene (6g) on hydrogenation of the double bond

Unsaturated compound	Saturated compound	Δ(δ) *	
		exo-H	*endo*-H
(1b) (*exo*-Cl)	(2b) (*exo*-Cl)	+0.12	−0.1
(1b) (*endo*-Cl)	(2b) (*endo*-Cl)	+0.23	−0.33
(6g)	(7e)	+0.08	−0.24

* + signifies an upfield shift, − a downfield shift.

Thirdly, it is well known that in norbornenes having an *exo*-halogen at C-5 or -6 significant deshielding of the 7-proton *syn* to halogen occurs in comparison with isomers in which the halogen is *endo*. There is usually little effect on the 7-proton *anti* to halogen.[8b] A similar effect would be expected in norbornane derivatives but has not been observed due to peak overlap. In Table 4, the H(7) shifts in (1b) are compared with examples from the work of LeBel [8b] and the results are clearly in agreement with the assignments above. In the saturated compound (2b), the marked downfield shift of H(7-*syn*) at δ 2.05 in the major invertomer corresponds with the *exo*-Cl assignment. The relatively high field position of H(7-*anti*) (δ 1.37) in this case is, of course, due to its position above a saturated two-carbon bridge as opposed to the unsaturated linkage in the other examples.

TABLE 4

Effect of *exo*- or *endo*-chlorine on geminal 7-protons

Compound	Chlorine configuration	Chemical shift (δ) H(7-*syn*)	H(7-*anti*)
(6a) [8b]	*endo*	1.47	1.75
(6e) [8b]	*endo*	1.42	1.77
(1b)	*endo*	1.58	1.58
(6b) [8b]	*exo*	2.05	1.77
(1b)	*exo*	2.22	1.80
(2b)	*exo*	2.05	1.37

The method of Shanan-Atidi and Bar-Eli [10] for obtaining free energies of activation from the coalescence temperature of an unequal doublet was applied, although values obtained using population-weighted values for lifetimes and the Gutowsky approximation gave results which agreed remarkably well (±0.2 kcal mol^{-1}) with the $\Delta G^‡$ values in Table 5. Maximum possible limits were estimated for the key parameters in Table 5. The quoted errors stem largely from uncertainty in T_c which has almost certainly been overestimated [see Experimental section] and the final quoted limits in $\Delta G^‡$ might therefore be considered unduly pessimistic.

DISCUSSION

The effect of ring size on the barrier to nitrogen inversion is illustrated in Table 6. There is a steady increase in the barrier as one moves from seven- to four-membered azamonocycles followed by the well known spectacular rise to aziridines. Addition of a second bridge in the examples studied by Lehn [2] appears to raise the barrier slightly relative to monocyclic examples but there are not enough data in the literature for detailed discussion.[1a] Barriers in the *N*-chloro-compounds quoted are higher by *ca.* 2—3 kcal mol^{-1} than in the *N*-methyl analogues.

The $\Delta G^‡$ values observed in the three amines in the present study confirm the anticipated trend. Replacement of the $-CH_2{\cdot}CH_2-$ bridge in (4b) by a shorter $-CH{=}CH-$ bridge in (3b) raises $\Delta G^‡$ as does replacement by a $-CH_2-$ bridge [(2b)]. A combination of both changes as in (1b) has an effect which is more than simply additive leading to a free energy of activation greater than in azetidines and lower only than aziridines and 7-azanorbornyl systems. The barrier unfortunately remains too low to allow study of the chemistry of the separate *exo*- and *endo*-isomers in solvolysis (*cf.* the all-carbon ana-

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[8] (*a*) P. Laszlo and P. von R. Schleyer, *J. Amer. Chem. Soc.*, 1964, **86**, 1171; (*b*) P. M. Subramanian, M. T. Emerson, and N. A. LeBel, *J. Org. Chem.*, 1965, **30**, 2624.

[9] R. R. Fraser, *Canad. J. Chem.*, 1962, **40**, 78.

[10] H. Shanan-Atidi and K. H. Bar-Eli, *J. Phys. Chem.*, 1970, **74**, 961.

logues), a goal which has only been achieved in the elegant work of Rautenstrauch on 7-chloro-7-azanorbornadienes.[3b]

Table 5

Invertomer populations, coalescence temperatures, and free energy data for inversion at nitrogen in the *N*-chloroamines (1b)—(3b)[f]

	(1b)	(2b)	(3b)
exo-Cl (%)[a]	12 ± 5 (−54 °C)	75 ± 5 (−84 °C)	9 ± 5 (−87 °C)
	19 ± 5 (+41 °C)	65 ± 8 (+24 °C)	15 ± 5 (+20 °C)
K_{eqm}[b]	0.14 ± 0.07 (−54 °C)	3.0 ± 1.0 (−84 °C)	0.10 ± 0.06 (−87 °C)
	0.23 ± 0.09 (+41 °C)	1.8 ± 0.5 (+24 °C)	0.18 ± 0.07 (+20 °C)
ΔG°/kcal mol^{-1}[c]	0.9 ± 0.2 (−54 °C)	−0.4 ± 0.2 (−84 °C)	0.9 ± 0.3 (−87 °C)
	0.9 ± 0.2 (+41 °C)	−0.4 ± 0.2 (+24 °C)	1.0 ± 0.3 (+20 °C)
$\delta\nu$ (Hz) H(3-*exo*)[d]	50 ± 19	44 ± 2	73 ± 2
$\delta\nu$ (Hz) H(3-*endo*)	110 ± 20	84 ± 2	71 ± 2
T_c/°C H(3-*exo*)	+15 ± 15	−30 ± 15	−50 ± 10
T_c/°C H(3-*endo*)	+15 ± 15	−30 ± 15	*e*
$\Delta G^\ddagger$ *endo* ⟶ *exo*/kcal mol^{-1} [H(3-*exo*)]	15.1 ± 1.2	11.9 ± 0.8	11.6 ± 0.8
[H(3-*endo*)][g]	14.6 ± 1.2	11.6 ± 0.8	*e*
$\Delta G^\ddagger$ *exo* ⟶ *endo*/kcal mol^{-1} [H(3-*exo*)]	14.2 ± 1.1	12.3 ± 1.0	10.7 ± 0.5
[H(3-*endo*)][g]	13.7 ± 1.0	12.0 ± 1.0	*e*

[a] Figures at low temperature are based on direct integration. Figures at the higher temperature use the assumption that peak positions are population-weighted means. Figures are based on separate calculations for H(3-*exo*) and H(3-*endo*) except for (1b) where the large uncertainty in major–minor separation for H(3-*exo*) will lead to unacceptable error limits. [b] For the equilibrium *endo*-Cl $\rightleftharpoons$ *exo*-Cl. [c] Free energy change from *endo*-Cl to *exo*-Cl. [d] Frequency separation between the signals due to the given proton in the major and minor invertomers. [e] No meaningful estimate of T_c was possible due to coincidence of H(3-*endo*) and a bridgehead proton. [f] Figures given are rounded off to a realistic accuracy level. Where error limits are not symmetrical about the probable value, the larger deviation is quoted as the error. The calculations were carried through without ' rounding off ' in order to avoid the introduction of artificial errors. [g] Averaged $\Delta G^\ddagger$ values are quoted in Table 6.

Table 6

Barriers to inversion at nitrogen in selected *N*-chloroamines

	$\Delta G^\ddagger$/kcal mol^{-1}	Temperature (°C)	Reference
N-Chloroperhydroazepine	8.4 ± 0.3	−100	2
3-Chloro-3-azabicyclo[3.2.2]nonane	10.1 ± 0.2	−65	2
(4b)	10.6 ± 0.2	−54	2
(3b)	11.6 ± 0.8 (*endo* ⟶ *exo*-Cl) 10.7 ± 0.5 (*exo* ⟶ *endo*-Cl)	−50	This work
(2b)	11.8 ± 0.9 (*endo* ⟶ *exo*-Cl) 12.2 ± 1.1 (*exo* ⟶ *endo*-Cl)	−30	This work
(1b)	14.8 ± 1.5 (*endo* ⟶ *exo*-Cl) 13.9 ± 1.3 (*exo* ⟶ *endo*-Cl)	+15	This work
N-Chloropyrrolidine	10.4	−68	*a*
N-Chloroazetidine	13.4	−20	11
N-Chloro-2,2-dimethylaziridine	>23	>180°	*b*

[a] J. B. Lambert and W. L. Oliver, *Tetrahedron Letters*, 1968, 6187. [b] J. M. Lehn and J. Wagner, *Chem. Comm.*, 1968, 148.

The simplest explanation for the observed increase is based on a gradual increase in angle strain along the series which raises the energy of the ' planar sp^2 ' transition state relative to the ' tetrahedral sp^3 ' ground states. The explanation may be couched in terms of variation in *s* character of the nitrogen lone pair. There is no firm basis on which to invoke any unusual destabilisation of the transition state relative to ground state in these systems in order to explain the higher $\Delta G^\ddagger$ values. It must be remembered, however, that unusual (and unexplained) effects have been observed in 7-azabicyclo-[2.2.1]-heptanes, -heptanes, and -heptadienes where $\Delta G^\ddagger$ inversion may reach 19.5—23.5 kcal mol^{-1} [1,3] despite the fact that the C–N–C bond angles are close to those in azetidines where $\Delta G^\ddagger$ inversion is lower by *ca.* 6—12 kcal mol^{-1}.[1,11] Significant stabilisation of one ground state configuration in the unsaturated examples (1) and (3) relative to the transition state due to a homoallylic interaction seems unlikely, at least in (1b) where ΔG° (which might reflect such an interaction) is much smaller than the observed increase in $\Delta G^\ddagger$ in either direction.

Turning to the question of invertomer ratios, the preference for *exo*-Cl over *endo*-Cl in (2b) must be steric in origin. The free energy difference $\Delta G^\circ = 0.4 \pm 0.2$ kcal mol^{-1} (at 24 °C) may be compared with the situation in 2-substituted norbornanes where a similar *exo*-preference is observed and ΔG° varies from 0.65 kcal mol^{-1} (at 75 °C) for a CO_2Me substituent to 1.38 kcal mol^{-1} (at 100 °C) for NO_2.[12] The lower value of ΔG° for a substituent attached to nitrogen is in qualitative agreement with the established ability of nitrogen to distort in order to relieve steric interactions (as shown, for example, by the conformational ΔG° for 1-methylpiperidine of 0.65 compared with 1.8 for methylcyclohexane [13]). The steric demands of the chlorine attached to nitrogen thus do not appear to be very great but it is clear from analysis of the

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[11] J. B. Lambert, W. L. Oliver, jun., and B. S. Packard, *J. Amer. Chem. Soc.*, 1971, **93**, 933.

[12] R. J. Oulette, J. D. Rawn, and S. N. Jreissaty, *J. Amer. Chem. Soc.*, 1971, **93**, 7117.

[13] R. A. Y. Jones, A. R. Katritzky, A. C. Richards, and R. J. Wyatt, *J. Chem. Soc. (B)*, 1970, 122.

temperature independent ^{1}H n.m.r. spectra of *N*-chloroderivatives of 1,7,7-trimethyl- and 4,7,7-trimethyl-2-azanorbornanes [14] that the introduction of a *syn*-7-methyl group effectively confines the chlorine to the *endo*-position.

In 5-substituted bicyclo[2.2.2]oct-2-enes, COMe, CO$_2$Me, and NO$_2$ groups shown an *endo* : *exo* preference of *ca.* 2.2—2.4 : 1 [15] providing a useful analogy with the *endo*-preference shown by Cl in (3b). The question of interaction between the π-system and nitrogen lone pair in (3) has been examined by Morishima and Yoshikawa whose contact shift studies on the NH compound (3a) suggested almost equal populations for the two invertomers.[5] Grutzner [16] has suggested that equal invertomer populations in (3a) argue strongly against significant stabilisation in the ground state and considers that the n.m.r. results [5] and photoelectron spectroscopy data [17] of Morishima are consistent with either a very small homoallylic interaction or alternatively with the presence of one major isomer having the lone pair *anti*(*exo*) to the π-system. In the case of the 3-methyl analogue (3c), the overwhelming predominance of the invertomer having the lone pair *exo*(*endo*-methyl) is shown by ^{1}H and ^{13}C n.m.r. contact shift studies at ambient temperature,[5] and the presence of one conformation over a wide temperature range is confirmed by ^{13}C [6] and ^{1}H n.m.r. [14] The observed preference in (3c) is attributed to a repulsive interaction between the *N*-methyl group and the protons of the two-carbon bridge [5] and a similar but smaller interaction would explain the behaviour of the *N*-chloro-analogue (3b).

No significant *exo* : *endo* preference emerges for the 5-CN and 5-CO$_2$Me groups in norbornenes.[18] With a 5-NO$_2$ or 5-OH substituent the *exo* : *endo* ratio reaches 1.18 and 4, respectively, being ascribed to a repulsion involving the π-system.[15,19] Whilst the comparison is somewhat crude, it seems reasonable to consider an electronic influence in any explanation of the *endo*-preference observed in (1b) but the simple fact that an equilibrium ***mixture*** is observed [as with (3b)] does argue against any really substantial interaction.

It is interesting to note that (3b), (3c), and (1b) have in common an *exo*-orientation of the nitrogen lone pair and the vinyl bridge. Indeed if the plausible argument [16] that (3a) may exist largely as a single isomer is correct, then this observation would apply to almost every 2-azabicyclo-[2.2.1]heptene and -[2.2.2]octene studied to date. The only apparent exceptions would then be found in the failure of Biehler and Fleury to observe two invertomers in the low-temperature ^{1}H n.m.r. spectrum of 2-substituted 3,3-dicyano-2-azabicyclo[2.2.1]hept-5-enes [20] which was attributed by these workers either to rapid inversion at low temperatures or to an almost 100% population of the invertomer with the nitrogen substituents (OSO$_2$C$_6$H$_4$Me, OBz) *exo* to the π-bond. In view of the discussion above it is possible that an almost 100% population of the *endo*-invertomer actually existed over the temperature range studied.

EXPERIMENTAL

N.m.r. spectra were measured using a JEOL JNM-PS-100 spectrometer. CFCl$_3$ was used as solvent throughout the n.m.r. studies, with tetramethylsilane as internal standard. The variable temperature controller was calibrated before and after use with a thermocouple inserted into the probe. Temperature reproducibility was within ±1 °C. Low-temperature n.m.r. spectra are illustrated in Figures 1—4 and relevant data are collected in Tables 1 and 5. It has been assumed in the calculations that ΔG° for such an intramolecular process is relatively insensitive to temperature and this is borne out by comparison of the ΔG° (low T) with ΔG° (high T) figures shown in Table 5. K_{eq} and ΔP were calculated for all permutations of T_c, ΔG°, and their limits and the final calculations of free energies of activation were performed for the most probable values and for the extreme values of the parameters in equations (1) and (2) [10] in order to give probable values for $\Delta G^‡$ in both directions together with upper and lower limits.

$$\Delta G_A^‡ = 4.57\left|\begin{array}{l} T_c \text{ min} \\ T_c \\ T_c \text{ max}\end{array}\right| \left[10.62 + \left|\begin{array}{l} Y^- \text{ min} \\ Y^- \\ Y^- \text{ max}\end{array}\right| + \log \left|\begin{array}{l} T_c \text{ min}/\delta\nu_{\text{max.}} \\ T_c/\delta\nu \\ T_c \text{ max}/\delta\nu_{\text{min.}}\end{array}\right|\right] \quad (1)\,^*$$

$$\Delta G_B^‡ = 4.57\left|\begin{array}{l} T_c \text{ min} \\ T_c \\ T_c \text{ max}\end{array}\right| \left[10.62 + \left|\begin{array}{l} Y^+ \text{ min} \\ Y^+ \\ Y^+ \text{ max}\end{array}\right| + \log \left|\begin{array}{l} T_c \text{ min}/\delta\nu_{\text{max.}} \\ T_c/\delta\nu \\ T_c \text{ max}/\delta\nu_{\text{min.}}\end{array}\right|\right] \quad (2)\,^*$$

* $Y^{\pm} = \log[x/2\pi(1 \pm \Delta P)]$.

It is evident that quoted errors in $\Delta G^‡$ stem largely from uncertainty in the coalescence temperature, T_c, for the signals due to H(3-*exo*) and H(3-*endo*). T_c could not easily be obtained directly from the spectra, due to their complexity, and the large difference in the size of the signals due to these protons in the *exo*- and *endo*-invertomers. Estimates were obtained from plots of the positions of the major and averaged signals due to H(3-*exo*) and/or H(3-*endo*) against temperature (*e.g.* Figure 5). In each case the coalescence temperature was taken as the mean of the temperature range over which the change from rapid to slow inversion occurred and the error as plus or minus half this range.

Solutions of the chloroamines in this work were prepared by a modification of the method of Graefe [7] by shaking a solution of the appropriate amine hydrochloride [4] (*ca.* 100 mg) in water (0.5 ml) with commercial sodium hypochlorite solution (*ca.* 12% available chlorine; 0.5 ml) for 5 min.

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[14] J. R. Malpass and M. P. Walker, unpublished results.

[15] T. J. Oulette and G. E. Booth, *J. Org. Chem.*, 1965, **30**, 423.

[16] J. B. Grutzner, *J. Amer. Chem. Soc.*, 1976, **98**, 6385.

[17] I. Morishima, K. Yoshikawa, M. Hashimoto, and K. Bekki, *J. Amer. Chem. Soc.*, 1975, **97**, 4283.

[18] J. M. Mellor and C. F. Webb, *Tetrahedron Letters*, 1971, 4025.

[19] C. F. Wilcox, M. Sexton, and M. F. Wilcox, *J. Org. Chem.*, 1963, **28**, 1079.

[20] J-M. Biehler and J-P. Fleury, *J. Heterocyclic Chem.*, 1971. **8**, 431.

Extraction with $CFCl_3$ (total *ca.* 1 ml) in the cold gave a solution of the *N*-chloroamine which was dried ($MgSO_4$, filtered, and evaporated under a stream of nitrogen to a suitable volume for use as an n.m.r. sample (*ca.* 0.5 ml).

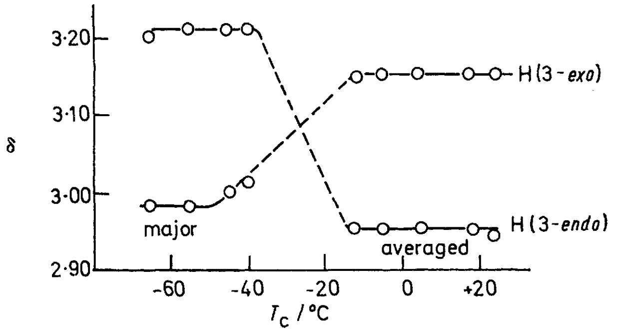

FIGURE 5 Coalescence temperatures for H(3-*exo*) and H(3-*endo*) in 2-chloro-2-azabicyclo[2.2.1]heptane (2b)

Preparation of 3,3-dideuterio-2-azabicyclo[2.2.1]hept-5-ene from 2-azabicyclo[2.2.1]hept-5-en-3-one followed exactly the procedure described in ref. 4 with $LiAlD_4$ in place of $LiAlH_4$, and using D_2O-ether in the work-up. The free amine formed a crystalline picrate and could be regenerated by treatment with dilute aqueous base and extraction into $CFCl_3$. N.m.r. absorptions at δ 3.77 and 1.9 [4] were absent, as expected, and integration confirmed the incorporation of $>98\%$ deuterium at the 3-*exo*- and 3-*endo*-positions. Conversion of the NH (or ND) amine to the *N*-chloro-compound (5) with hypochlorite followed the general method above.

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