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NMR Studies of N-Methyl Derivatives of the 2-Azabicyclo-[2.2.1]heptyl and -[2.2.2]octyl Ring Systems; Kinetic Protonation in Determination of Invertomer Preferences

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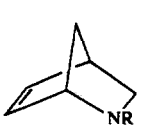
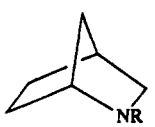
Abstract *The title compounds were studied by ^{1}H, ^{13}C, and ^{15}N NMR spectroscopy. Since inversion at nitrogen is rapid on the NMR time scale even at low temperatures, kinetic protonation was used to estimate invertomer ratios at ambient temperature. Invertomer preferences appear to be consistent with the operation of steric factors.*

Introduction

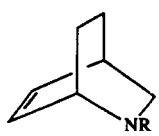
We are currently investigating facial selectivity in cycloaddition reactions of unsaturated azabicyclic ring systems including the influence of nitrogen in attack on the π-bond.[1] The multicyclic products of these reactions give complex NMR spectra and we found limited information on structure/J value correlations from published reports of N-alkyl derivatives of unsaturated bicyclic amines such as **(1)** and **(3)**, in sharp contrast to the wealth of information on carbocyclic analogues.[2] We also required information on the configuration at nitrogen in the chosen substrates in order to assess any influence of nitrogen on selectivity. Our cycloaddition studies include reactions of 7-azabicyclo[2.2.1]heptene derivatives where invertomer preferences are well established[3] and where the nitrogen is symmetrically disposed with respect to the π system. However, in the case of 2-azabicyclo[2.2.1heptenes **(1)** and -[2.2.2]octenes **(3)** (in which the nitrogen is unsymmetrically disposed in relation to the double bond) the available inversion studies are selective and qualitative; the amine **(5)** has not been reported. We have therefore prepared and recorded ^{1}H, ^{13}C and ^{15}N NMR spectra of the N-methyl compounds **(1)** - **(6)** and have completed first-order analyses of their ^{1}H spectra. Kinetic protonation studies and detailed assignments of the spectra of the quaternary salts have allowed the estimation of invertomer preferences.



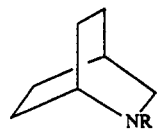
R=CH_3 **(1a)**
R=H **(1b)**
R=Cl **(1c)**



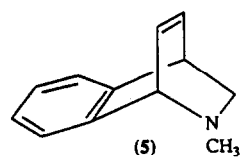
(2a)
(2b)
(2c)



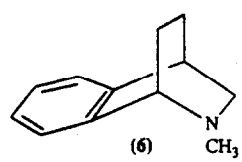
(3a)
(3b)
(3c)



(4a)
(4b)
(4c)



(5) CH_3



(6) CH_3

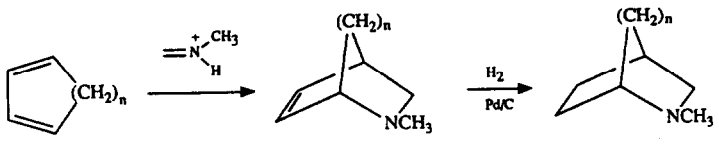
In earlier studies, we explored the preparation of secondary 2-azabicyclo[2.2.1]heptanes (**2b**) and hept-5-enes (**1b**), together with 2-azabicyclo[2.2.2]octanes (**4b**) and oct-6-enes (**3b**)[4] as precursors of N-chloro- derivatives of these ring systems (**1c**) - (**4c**);[5] VT NMR studies of the N-chloroamines led to measurement of nitrogen inversion barriers and invertomer preferences.[6] In the absence of the 'heteroatom' effect[7] of chlorine, inversion barriers for the N-alkyl amines (**1a**) - (**4a**) are reduced below the range normally accessible by VT NMR. These lower barriers contrast with the situation for 2,3-diazabicyclo[2.2.1]heptenes where inversion can be slowed sufficiently for NMR analysis,[8] and also N-alkyl and N-chloro derivatives of 7-azabicyclo[2.2.1]heptanes and heptenes[3] where inversion barriers are anomalously high.

Some earlier investigations of configurational preferences at nitrogen have been reported in the series (**2**) - (**4**) but different approaches were used and results have been qualitative in almost all cases. In studies of steric crowding in the *endo*- cavity of the norbornane system, Menger investigated a range of N-alkyl derivatives of (**2**)[9] and demonstrated little difference between the energies of the *exo*- and *endo*- quaternary salts of (**2a**) formed by protonation in aqueous acid but no unsaturated derivatives were studied. Proposals concerning the influence of homoallylic interactions on the preferred orientation of the nitrogen lone pair have been made for (**3a**) by Morishima on the basis of indirect lanthanide shift studies[10a] and *ab initio* calculations have been carried out on the 2-azabicyclo[2.2.2]octane system.[11] The sole value for a nitrogen inversion barrier in an N-alkyl derivative of these ring systems was reported for (**4a**).[12] This was reassessed by Nelsen[13] who also performed low-temperature ^{13}C NMR studies of (**3a**) in which only one conformation was visible at low temperature; the lack of chemical shift sensitivity suggested that the same conformation dominates even at higher temperatures.[13] Kinetic protonation[14] of (**3a**) and a deuteriated derivative of (**6**) has been reported;[15] proposed preferences were based on relative shifts of the N-methyl signals in the complex ^1H NMR spectra, but detailed spectral analysis was not possible and quantitative results were not obtained.

Our own studies failed to demonstrate changes in the ^1H NMR spectrum of (**1a**) at temperatures down to 153 K. We therefore turned to kinetic protonation at ambient temperature to estimate invertomer preferences for (**1a**) and (**3a**) and extended the study to (**2a**) - (**6**). We have completed detailed analysis of high resolution ^1H and ^{13}C NMR spectra of the free and protonated amines and have included ^{15}N NMR data for amines and protonated amines in order to allow comparison with other nitrogen-bridged systems, some of which have unusual ^{15}N spectra.[16]

Preparation

The amine (**1a**) was made by addition of the N-methyliminium salt to cyclopentadiene as shown in scheme 1.[17a] We used the same method[17b] for the preparation of (**3a**) from cyclohexa-1,3-diene in 18% yield. The alternative approach[4] based on addition of chlorosulphonyl isocyanate to cyclohexa-1,3-diene followed by sequential hydrolytic removal of the N-chlorosulphonyl group, reduction with lithium aluminium hydride, and N-methylation was more efficient overall but was less convenient. Catalytic hydrogenation provided (**2a**) and (**4a**) (scheme 1).



Scheme 1

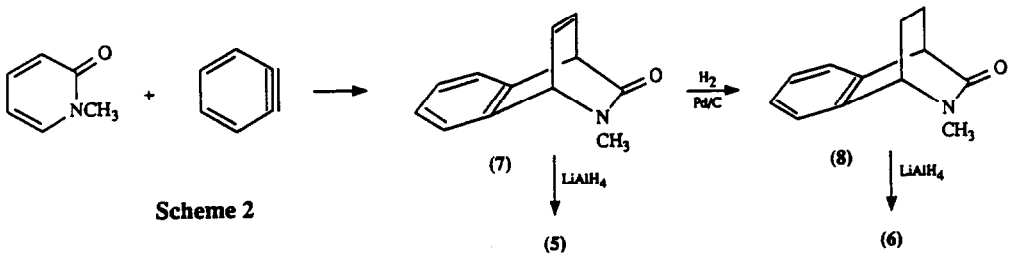
n=1
n=2

(**1a**) n=1
(**3a**) n=2

(**2a**) n=1
(**4a**) n=2

The lactam (**7**) was made by a modification of the literature method[18] to give a product which was

significantly cleaner and easier to purify. Reduction of the lactam (**7**) with lithium aluminium hydride gave the amine (**5**) but this was unfortunately sensitive to acid and heat. It was stable for at least a day if kept cold and in a basic environment but it decomposed spontaneously in acid,[17c] giving naphthalene. Hydrogenation of (**7**) gave the saturated lactam (**8**); hydride reduction afforded (**6**).



Scheme 2

Results and Discussion

^1H and ^{13}C NMR spectra of N-methyl amines (1-4a), (5) and (6)

A detailed analysis of the NMR spectra of (**1a**) and (**2a**) is incorporated into tables 1 and 2 respectively. The substantial chemical shift difference between *exo*- and *endo*- H_3 (1.81 δ) is greater than in norbornene[20] and suggests an unequal invertomer population. The correct assignment of the H_3 signals is important as a basis for protonation studies and follows from the vicinal coupling to H_4 which is greater for H_{3x} (3.0 Hz) than for H_{3n} (≈ 0 Hz). This is in agreement with earlier work on (**1c**) ($J_{3x,4}$ = 3.0 Hz)[6] and norbornene ($J_{3x,4}$ = 3.5 Hz);[20] in both of these cases, the value for $J_{3n,4}$ also approaches 0. The observation of substantial W-coupling $J_{3n,7a}$ in (**1a**) confirms the assignment of H_{3n}. Homonuclear double resonance experiments established the major vicinal couplings unambiguously and distinguished between H_5 and H_6; small W-coupling $J_{1,4}$[4,8] was also indicated.

The ^1H NMR spectrum of (**2a**) was analysed with the aid of a COSY spectrum ($^1H\delta$ *v* $^1H\delta$) and selective spin-decoupling experiments. The geminal protons on C_3 were distinguished by coupling to H_4 ($J_{3x,4}$ = 3.3 Hz; $J_{3n,4}$ = too small to be resolved) and by W-coupling ($J_{3x,5x}$ = 3.3 Hz; $J_{3n,7a}$ = 1.0 Hz).

^1H NMR chemical shift data for (**3a**) and (**4a**) have been reported earlier but without any coupling data.[10a] Our detailed analysis is incorporated into table 3 which also summarises spectra for the diastereoisomeric protonated amines. Selected data for (**5**) and (**6**) are included in table 4.

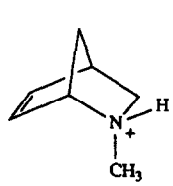
Protonation of N-methyl amines (1-4a) and (6)

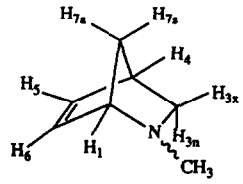
The kinetic protonation technique has been used in a range of amines including piperidines,[14] amines which possess lower barriers to inversion at nitrogen than those studied here. The rate of protonation by strong acid is considered to be diffusion-controlled in homogeneous solution and the ratio of salts produced should reflect directly the thermodynamic invertomer ratio in the free amine. Our confidence in the reliability of this technique was increased by work with derivatives of the 7-azabicyclo[2.2.1]heptene system where our results from direct integration at low temperatures[3a] were in good agreement with earlier invertomer ratios obtained by Marchand using kinetic protonation.[15]

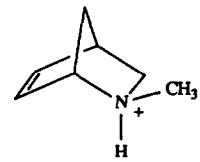
Amines were added to solutions of trifluoroacetic acid in $CDCl_3$ (ratio 1:4)[15] at ambient temperature; ^1H and ^{13}C NMR spectra were recorded immediately. The ratios were unchanged after standing for 48h. Protonation of (**1a**) leads generally to downfield shifts of signals in the ^1H NMR spectra; an exception is seen for H_{3x} in the *exo*-methyl salt where there is an upfield shift associated with the eclipsing N-methyl group. In the corresponding *endo*-methyl salt, the downfield shift of H_{3n} is attenuated similarly. Protonation at nitrogen gives an additional point of stereochemical reference since vicinal HC-NH coupling is now observed in the ^1H NMR spectrum. Thus in the data for (**1aH$^+$**) (table 1), each methyl signal now appears as a doublet ($J_{NH,Me}$ = 5.4 Hz) and, more importantly, the *cis*- relationship between H_{3x} and NH_x in the *endo*-methyl salt

and between H_{3n} and NH_n in the *exo*- methyl salt is indicated by a J value of 6.6 Hz in each case. The respective values for $J_{3n,NHx}$ and $J_{3x,NHn}$ are smaller (3.6 Hz) and the stereochemistry of protonation is thus defined. ^{13}C NMR spectra for (**1aH⁺**) are also summarised in table 1 together with comparison data for the (rapidly inverting) free amine. The correlation of ^{1}H and ^{13}C signals for (**1aH⁺**) was confirmed with the aid of a 2D experiment. This allowed assignment of each carbon and, in particular, C_5 and C_6 in (**1a**). Typical ^{13}C compression shifts (γ-effect) are shown by C_7 in the *exo*-methyl salt (δ 44.5) which appears upfield of the *endo*- isomer (δ 48.3).

Table 1. NMR Data for (1a) and its protonated forms.





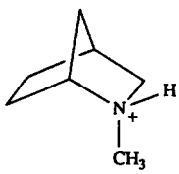


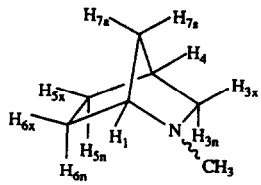
^{1}H NMR δ	(**1aH⁺**) major *endo*-methyl	(**1a**) free amine	(**1aH⁺**) minor *exo*-methyl
H_1	4.67 brs	3.73 brs	4.40 brs
H_{3x}	3.80 ddd	3.16 dd	2.94 ddd
H_{3n}	2.20 ddd	1.35 dd	3.18 ddd
H_4	3.40 brs	2.88 brs	3.43 brs
H_5	6.88 ddd	6.30 ddd	6.65 ddd
H_6	6.32 dd	6.02 dd	6.38 dd
H_{7s}	1.97 brd	1.58 ddd	2.02 brd
H_{7a}	1.93 brd	1.39 dddd	1.92 brd
NCH_3	2.64 d	2.16 s	3.01 d
Selected Spin-spin Coupling Constants (Hz)			
$J_{1,5}$	1.2	1.0	1.2
$J_{1,6}$	3.0	2.0	3.0
$J_{1,7s}$		1.8	
$J_{1,7a}$		1.6	
$J_{3x,3n}$	10.5	8.4	10.5
$J_{3x,4}$	3.0	3.0	2.7
$J_{3n,7a}$	2.4	1.6	2.1
$J_{4,5}$	2.9	3.0	2.9
$J_{4,6}$	<1	<1	<1
$J_{4,7s}$		1.2	
$J_{4,7a}$		1.4	
$J_{5,6}$	5.5	5.7	5.5
$J_{7s,7a}$	9.0	7.9	9.0
$J_{NH,3x}$	6.6		3.6
$J_{NH,3n}$	3.6		6.6
$J_{NH,Me}$	5.4		5.4
^{13}C NMR δ	(**1aH⁺**) major *endo*-methyl	(**1a**) free amine	(**1aH⁺**) minor *exo*-methyl
C_1	70.3	66.4	71.7
C_3	53.7	53.7	55.1
C_4	43.8	44.8	43.7
C_5	144.9	136.2	142.8
C_6	128.3	130.7	132.5
C_7	48.3	49.0	44.5
CH_3	38.9	41.2	41.7

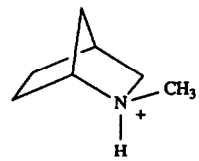
Spectra in $CDCl_3$ (298 K). J values by inspection assuming first-order behaviour; est. errors ca. ± 0.3 Hz.

Similar methods were applied to (**2aH⁺**) and the data are summarised in table 2. Values of J follow the pattern described above including the higher values (6.0 Hz) for $J_{NHx,3x}$ in the endo-methyl salt and for $J_{NHn,3n}$ in the exo-methyl isomer corresponding to an 'in-line' relationship between the NH and the appropriate vicinal neighbour. Once again, the marked upfield shifts of H_{3x} in the major isomer and H_{3n} in

Table 2. NMR Data for (2a) and its protonated forms.







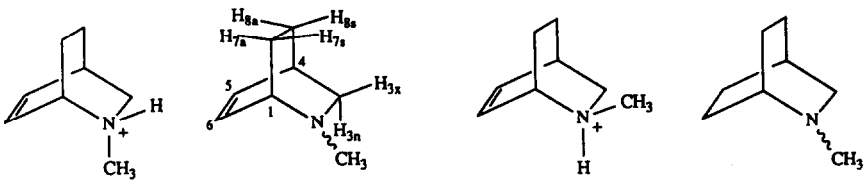
^{1}H NMR δ	(2aH⁺) minor *endo*-methyl	(2a) free amine	(2aH⁺) major *exo*-methyl
H_1	4.03 brs	3.08 brs	3.87 brs
H_{3x}	3.71 dddd	2.70 ddd	2.85 [a]
H_{3n}	2.55 ddd	2.20 dd	3.60 ddd
H_4	2.70 brs	2.30 brs	2.77 brs
		H_{5x} 1.51 ddddd	
		H_{5n} 1.26 ddddd	
$H_{5,6,7}$	1.5 - 2.1 m	H_{6x} 1.39 ddddd	$H_{5,6,7}$ 1.5 - 2.1 m
		H_{6n} 1.75 ddddd	
		H_{7s} 1.66 ddddd	
		H_{7a} 1.22 dddd	
NCH_3	~2.8	2.30 s	2.83 d
Spin-spin Coupling Constants (Hz)			
$J_{3x,3n}$	10.5	9.0	10.5
$J_{3x,4}$	~3.5	3.3	[a]
$J_{3x,5x}$	~3.5	3.3	[a]
$J_{3n,4}$	not resolved	not resolved	not resolved
$J_{3n,7a}$	2.0[b]	1.0	2.0[b]
$J_{NH,3x}$	6.0[c]	$J_{1,4}$ <1.0 $J_{5x,5n}$ ~11.5	$J_{NH,3x}$ [a]
$J_{NH,3n}$	3.5[c]	$J_{1,6x}$ 3.3 $J_{5x,6n}$ ~3.3	$J_{NH,3n}$ 6.0[c]
$J_{NH,Me}$	[a]	$J_{1,6n}$ <1.0 $J_{5x,6x}$ ~11.5	$J_{NH,Me}$ 6.0
		$J_{1,7s}$ ~1.5 $J_{5n,6x}$ ~3.3	
		$J_{1,7a}$ ~1.0 $J_{5n,6n}$ ~10.0	
		$J_{4,5x}$ 4.0 $J_{5n,7s}$ 2.4	
		$J_{4,5n}$ <1.0 $J_{6x,6n}$ ~11.5	
		$J_{4,7s}$ ~1.5 $J_{6n,7s}$ 2.4	
		$J_{4,7a}$ ~1.0 $J_{7s,7a}$ 9.0	

^{13}C NMR δ	(2aH⁺) minor *endo*-methyl	(2a) free amine	(2aH⁺) major *exo*-methyl
C_1	65.5	62.7	67.5
C_3	60.8	61.2	62.8
C_4	37.1	38.3	37.2
C_5[d]	27.2	28.7	26.9
C_6[d]	21.3	26.4	25.5
C_7	37.8	35.7	34.3
CH_3	37.3	41.5	42.8

Spectra in $CDCl_3$ (298 K). J values by inspection assuming first-order behaviour; est. errors ca. ± 0.3 Hz.
a. Hidden beneath the major N-methyl signal b. Tentatively assigned by analogy with (**1aH⁺**)
c. By comparison with an experiment using CF_3COOD d. These assignments may be reversed.

the minor isomer are consistent with the presence of an eclipsing N-methyl group. It is not easy to assign C_5 and C_6 in the ^{13}C NMR with certainty but the assignments shown in table 2 are consistent with the larger upfield shift (γ-effect) being due to C_6 in the *endo*-methyl salt rather than C_5. The upfield shift experienced by C_7 in the *exo*-methyl isomer can similarly be ascribed to the effect of the nearby N-methyl group.

Table 3. NMR Data for (3a), (4a) and selected protonation data



^1H NMR δ	(3aH⁺) major *endo*-methyl		(3a) free amine		(3aH⁺) minor *exo*-methyl		(4a) free amine
H_1	4.10	brd	3.31	brs	4.03	brd	2.47 brs
H_{3x}	3.75	ddd	3.07	dd	a		2.70 brs
H_{3n}	2.90	m	1.89	ddd	a		)
H_4	2.90	br	2.50	brs	a		)
H_5 [b]	6.75	brdd	6.39	ddd	6.61	brt	)
H_6 [b]	6.38	brdd	6.25	ddd	6.47	ddd	)
H_{7s}	2.32	m	2.03	dddd	a		} 1.2 -2.0 m
H_{7a}	1.76	dddd	1.52	dddd	a		)
H_{8s}	1.52	dddd	1.35	dddd	a		)
H_{8a}	1.38	ddddd	1.13	ddddd	a		)
NCH_3	2.64	d	2.23	s	a		2.35 s
Selected Spin-spin Coupling Constants (Hz)							
$J_{1,5}$	~1		1.3		~1		
$J_{1,6}$	6		6.5		6		
$J_{3x,3n}$	11.4		9.7				
$J_{3x,4}$	2.1		2.1				
$J_{3n,4}$			2.6				
$J_{3n,8a}$			2.6				
$J_{4,5}$	6.5		5.4		6.5		
$J_{4,6}$	~1		1.3		~1		
$J_{5,6}$	7.5		8.2		7.5		
$J_{NH,3x}$	6.6		$J_{1,7a} = J_{1,7s} = J_{7s,8a} = 3.2$				
$J_{NH,Me}$	5.1		$J_{4,8a} = J_{4,8s} = 3.5$				
			$J_{7a,7s} = 10$; $J_{7a,8s} = 2.6$				
			$J_{7a,8a} = J_{7s,8s} = J_{8a,8s} = 12$				

^{13}C NMR δ	(3aH⁺) minor *endo*-methyl	(3a) free amine	(3aH⁺) major *exo*-methyl	(4a)	(4aH⁺)
C_1	54.6	53.6	53.6	51.0	54.0
C_3	54.1	56.0	53.6	57.5	56.5
C_4	28.3	30.5	28.1	25.6	23.7
C_5 [b]	137.6	133.1	135.7	)	) 23.5
C_6 [b]	125.8	130.9	129.9	} 24.5	} 22.8
C_7 [b]	22.2	26.1	20.8	} 23.5	} 21.6
C_8 [b]	18.5	21.1	16.9	)	) 18.7
CH_3	42.6	44.6	39.9	42.6	41.3

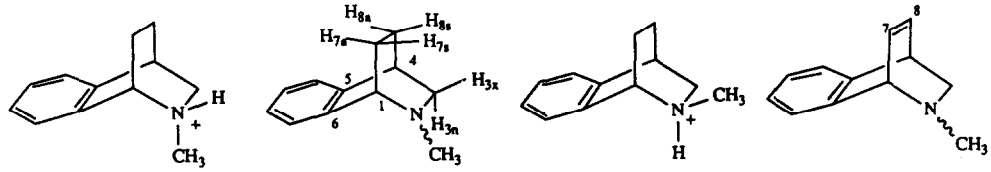
Spectra in $CDCl_3$ (298 K). J values by inspection assuming first-order behaviour; est. errors ca. ± 0.3 Hz

a. Signals due to the minor isomer could not be assigned with confidence

b. Based on assignments for the free amine in reference 10a

Data for (**3aH⁺**) and (**6H⁺**) are given in tables 3 and 4 respectively. The ^{1}H NMR analysis for the minor isomers is incomplete in some cases due to peak overlap but the large (*ca.* 7Hz) value for $J_{3x,NH}$ in each of the major isomers confirms the stereostructures shown; the additional ^{13}C data lead to an unambiguous conclusion in each case. Protonation experiments were not performed for (**5**) which decomposes too rapidly in acid.

Table 4. NMR Data for (6) and its protonated forms, and for (5).[a]



^{1}H NMR δ	(6aH⁺) major *endo*-methyl		(6) free amine		(6aH⁺) minor *exo*-methyl		(5) free amine	
H_1	4.55	brs	3.57	brdd	e		4.37	dd[c]
H_{3x}	4.02	ddd	3.26	dd	e		2.60	dd[d]
H_{3n}	~2.5[b]	m	1.88	ddd	e		2.24	dd[d]
H_4	3.39	brs	2.91	brs	e		3.79	ddd[c]
H_{7s}	2.55[b]	m	2.20	dddd	e	H_7	6.60	ddd[c,d]
H_{7a}	2.01	dddd	1.88	dddd	e			
H_{8s}	1.64	dddd	1.40	dddd	e	H_8	6.66	ddd[c,d]
H_{8a}	1.53	ddddd	1.32	ddddd	e			
NCH_3	2.48	d	2.02	s	3.08 d		2.16	s
Aryl	7.40	m	7.05 - 7.2 m		e		7.05 - 7.2 m	
Selected Spin-spin Coupling Constants (Hz)								
$J_{3x,3n}$	11.4		9.9				8.8	
$J_{3x,4}$	2.0		2.1				2.2	
$J_{3n,4}$	b		2.4				2.2	
$J_{3n,8a}$	b		2.4					
$J_{NH,Me}$	4.7				4.8			
$J_{NH,3x}$	7.0							
			$J_{1,7a} = 2.6$; $J_{1,7s} = 3.5$				$J_{7,8}$ 7.5	
			$J_{4,8a} = J_{4,8s} = J_{7a,8s} = 3$				$J_{1,7}$ 5.6	
			$J_{7a,7s} = 11$; $J_{7s,8a} = 3.2$				$J_{1,8}$ 1.7	
			$J_{7a,8a} = J_{7s,8s} = J_{8a,8s} = 11.7$				$J_{4,8}$ 5.9	
							$J_{4,7}$ 1.7	
^{13}C NMR δ	(6aH⁺) major *endo*-methyl		(6) free amine		(6aH⁺) minor *exo*-methyl		(5) free amine	
C_1	59.6		57.8		58.7		61.5	
C_3	56.4		57.0		55.8		54.3	
C_4	32.7		34.7		32.9		40.9	
C_7[d]	23.7		27.4		22.6		135.4	
C_8[d]	20.8		22.7		18.6		134.5	
CH_3	43.1		44.6		40.8		44.0	
Aryl	139.8	C	141.4	C	139.0	C	142.0	C
	131.9	C	139.3	C	135.5	C	140.8	C
	130.4	CH	126.7	CH	129.9	CH	125.6	CH
	127.9	CH	125.6	CH	127.6	CH	125.0	CH
	126.6	CH	124.2	CH	125.0	CH	123.5	CH
	124.6	CH	123.2	CH	124.5	CH	122.5	CH

Spectra in $CDCl_3$ (298 K). J values by inspection assuming first-order behaviour; est. errors ca. ± 0.3 Hz
a. Compound (5) decomposed on acidification **b.** Partly hidden by *endo*-N-methyl signal
c. Broadened slightly by allylic coupling: $J_{1,8}$ & $J_{4,7}$ < 1Hz **d.** These assignments may be reversed
e. Signals due to the minor isomer could not be assigned with confidence

Invertomer ratios

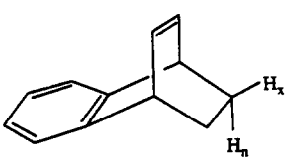
The ratios of stereoisomeric quaternary salts are shown in table 5 and show good agreement between values obtained using ^1H and ^{13}C NMR. Table 5 also includes data for the corresponding N-chloroamines which were obtained earlier by direct integration of signals due to the two invertomers at low temperature.[6]

Table 5. Invertomer Ratios

	R = Me (ratios from kinetic protonation) *endo-/exo-* ratio		R = Cl (from direct measurement) *endo-/exo-* ratio
Amine	**^1H NMR**	**^{13}C NMR**	**^1H NMR**
(1)	77 : 23	76 : 24	88 : 12 (at -54°C) 81 : 19 (at 41°C)
(2)[a]	24 : 76	24 : 76	25 : 75 (at -84°C) 35 : 65 (at 24°C)
(3)[b,c]	88 : 12	89 : 11	91 : 9 (at -87°C) 85 : 15 (at 20°C)
(6)[c]	89 : 11	92 : 8	--

a. Menger has quoted a ratio of 28 : 72 in H_2O at pH < 2.[9]
b. A preference for the *endo*-methyl invertomer in the free amine was inferred from work with lanthanide shift reagents.[10a]
c. A qualitative *endo*-methyl preference was proposed for (3) and deuteriated (6).[15]

The invertomer ratio could not be measured for (5) due to its instability in acid. Nevertheless it can be deduced that the equilibrium is not displaced very far from a 50:50 ratio since the chemical shift difference between H_{3x} and H_{3n} is small ($\Delta\delta$ = 0.36 ppm); table 4) and compares with a $\Delta\delta$ value of 0.1 ppm in the corresponding hydrocarbon, (9).[21] The upfield shift expected when a proton is eclipsed by a methyl group[22] would lead to a greater $\Delta\delta$ between H_{3x} and H_{3n} in (5) if the equilibrium was heavily weighted. Such an effect is seen in the case of (6) where there is a heavy preference for the *endo*- invertomer (table 5) and where H_{3n} (*syn*- to the benzo ring) is substantially upfield of H_{3x} ($\Delta\delta$ = 1.38 ppm) in agreement with the greater influence of the *endo*- N-methyl substituent in the free amine on a time-weighted basis.



(9)

The ratios in table 5 are consistent with expectations based simply on steric effects. In the amine (2a), the major invertomer has the methyl group *exo*- due to the destabilising steric interactions between the *endo*-methyl and the ethano bridge in the minor invertomer. In the unsaturated amines (1a), (3a) and (6a), the *endo*- methyl invertomers are preferred in agreement with reduced steric interactions with the etheno (or benzo) bridge compared with the ethano bridge. It seems unlikely that non-bonded n-π transannular interactions[10] have a major net influence on the invertomer preferences in these systems in agreement with earlier studies by Underwood,[23a] Grutzner[23b] and ourselves[3] where the stabilisation associated with lone-pair-π interactions was shown to be minimal. This conclusion is supported by the close similarities (table 5) between the ratios for the N-methyl amines and those observed directly for the corresponding N-chloro amines where the character of the lone pair is very different. The invertomer ratios in table 5 may well have relevance to other reactions involving quaternisation at nitrogen. Thus, a recent paper from Grieco[17d] describes a fragmentation reaction of (1) (R = benzyl) which requires *endo*- complexation by

9-BBN. Significantly, 20-25% of unchanged starting material was recovered even with an excess of 9-BBN; this corresponds to the proportion of *exo*- complex which might reasonably be expected from our results (23% *exo*- for R=Me[24]) and which would be unable to fragment.

^{15}N NMR spectra of amines (1-4a), (5) and (6) and lactams (7) and (8)

The ^{15}N chemical shift values observed for the bicyclic amines and lactams in this study are within the normal ranges established for cyclic analogues (table 6) and serve to emphasise the very unusual situation in 7-azabicyclo[2.2.1]heptyl systems where a tertiary nitrogen is deshielded substantially (by 40 - 95 ppm).[16] The values for (**1a**), (**3a**) and (**6**) are very similar, reflecting the similar structures and invertomer preferences (*endo*- methyl). By comparison, the saturated amine (**2a**) shows a modest downfield shift (c.f. values for 1-methylpyrrolidine and 1-methylpiperidine, table 6) and the amine (**5**) an intermediate value. However, it is not possible to say whether these shifts are a function of differences in invertomer preferences [*exo*- methyl for (**2a**) and little, if any, preference for (**5**)] or whether the more complex effects which are known to influence ^{15}N chemical shifts in cyclic amines[25a] are responsible. The upfield shift resulting from incorporation of an etheno- bridge into (**2a**) to give the homoallylic amine (**1a**) ($\Delta\delta$ = -6.7 ppm) is, however, mirrored qualitatively in the change from piperidine to 3-piperideine ($\Delta\delta$ = -10.1 ppm).[26]

Protonation shifts

Protonation of the amines (**1a**), (**2a**), (**3a**) and (**6**) leads to deshielding, the downfield shifts ranging from 14.1 to 26.4 ppm. The signal for the *exo*-methyl salt is slightly downfield of the *endo*- isomer for these compounds. Protonation of acyclic amines is known to lead to deshielding and slight deshielding is also generally observed for cyclic amines.[25b]

Table 6. ^{15}N Chemical Shifts for Free Amines/Lactams and for Amine Salts[a]

Compound	*endo*-methyl salt	free amine/lactam	*exo*-methyl salt
(1a)	-325.2	-348.2	-322.6
(2a)	-327.1	-341.2[b]	-324.3
(3a)	-332.9	-348.9	-332.5
(4a)	-336.3		-336.3
(5)		-345.6[b]	
(6)	-331.5	-349.4	-330.9
(7)		-263.5	
(8)		-260.7	
	HCl salt	**free amine/lactam**	
(1b)[c]	-332.7		
1-methylpyrrolidine[d]		-339.5	
1-methylpiperidine[d]		-343.5	
2-pyrrolidone[e]		-263.3	
2-piperidone[e]		-264.7	
1-methyl-2-piperidone[f]		-270.6	

a. Measurements on samples at natural abundance at 300 K in $CDCl_3$ in 10 mm tubes (chemical shift values in ppm relative to neat CH_3NO_2 contained in an internal, coaxial 5 mm tube). Protonated amine spectra obtained by addition of the amine to TFA (1.3 mol. equiv.) in $CDCl_3$ solution.

b. Spectrum recorded at 253 K

c. Spectrum recorded in H_2O/D_2O[27]

d. Spectrum recorded in C_6D_6[28]

e. Measured in CCl_4[29]

f. Measured in C_6D_6 [30]

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Experimental

Reactions were performed under dry nitrogen using solvents dried by standard methods. Magnesium sulphate was used to dry organic extracts prior to evaporation of solvent.

NMR spectra were measured in $CDCl_3$ with tetramethylsilane (TMS) as internal reference unless indicated otherwise. ^1H NMR spectra were recorded on Varian EM 390 (90 MHz) or Bruker AM 300 (300 MHz) spectrometers. ^{13}C NMR spectra (including routine DEPT spectra) were recorded on a Bruker AM 300 spectrometer at 75 MHz. ^{15}N NMR spectra were recorded on a Bruker AM 300 spectrometer at 30.4 MHz and were accumulated using the acquisition parameters recorded in reference 16.

Routine mass spectra were measured on a VG Micromass 14 spectrometer.

Melting point measurements were made using a Kofler hot stage apparatus and are uncorrected.

Protonation experiments were carried out by addition of each amine to 2 molar equivalents of trifluoroacetic acid in $CDCl_3$ (ratio 1:4)[15] at ambient temperature and the ^1H and ^{13}C NMR spectra were recorded immediately. The ratios recorded 48h later were similar.

2-Methyl-2-azabicyclo[2.2.1]hept-5-ene (1a)

Methylamine hydrochloride (1.75 g; 26.0 mmol) was dissolved in distilled water (10 ml). Methanal (2.95 g; 36.0 mmol) was added and stirred for 30 min. Freshly distilled cyclopentadiene (3.42 g; 52.0 mmol) was added to give a heterogeneous mixture which was stirred for 4 h at room temperature. The mixture was extracted twice with diethyl ether to remove the excess of cyclopentadiene. The aqueous layer was basified with 1M sodium hydroxide solution and extracted with $CFCl_3$. The organic layer was dried over $MgSO_4$ and the solvent was carefully removed under vacuum to leave (**1a**) as a yellow oil (2.26 g, 80 %) (lit. 82 % [17a]) which was passed through a short column of alumina using diethyl ether as eluant. NMR data are in table 1.

2-Methyl-2-azabicyclo[2.2.1]heptane (2a)[9,31]

The amine (**1a**) (1.0 g; 9.17 mmol) was dissolved in diethyl ether (35 ml) and Pd/C catalyst was added. A balloon of hydrogen was fitted to the reaction flask. The mixture was stirred for 6 h; the catalyst was removed by filtration through celite and was washed with diethyl ether. The solvent was removed under vacuum to give (**2a**) as a pale yellow oil (0.91 g, 90 %) which was passed through a short column of alumina using diethyl ether as eluant. NMR data are summarised in table 2.

2-Methyl-2-azabicyclo[2.2.2.]oct-5-ene (3a)

Methylamine hydrochloride (1.0 g; 12.5 mmol) was dissolved in water (5 ml). Methanal 37% (1.8 g; 16.3 mmol) and cyclohexa-1,3-diene (1.5 g; 18.8 mmol) were added to it in a Youngs tube. The tube was sealed, stirred and heated at 100°C in an oil bath for 84 h. The mixture was extracted twice with diethyl ether and the aqueous layer was then basified with 1M sodium hydroxide and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried over $MgSO_4$ and the solvent was removed under vacuum to give a brown oil. The compound was purified on silica using diethyl ether saturated with ammonia as eluant to give (**3a**) as a yellow oil (0.27 g, 18 %). Spectroscopic data were in agreement with those for a sample prepared[10a,13] using the method of Cava.[32] NMR data are summarised in table 3.

2-Methyl-2-azabicyclo[2.2.2]octane (4a)

Amine (**3a**) (0.2 g; 1.62 mmol) was dissolved in diethyl ether (25 ml) and hydrogenated over Pd/C as described for (**2a**) to give (**4a**) as a yellow pale oil (0.16 g, 80%). Spectroscopic data were in agreement with

those for a sample prepared[10a,13] using the method of Cava.[32] NMR data are summarised in table 3.

2-Methyl-5,6-benzo-2-azabicyclo[2.2.2]oct-7-ene (5)

Lactam (7) (0.13 g; 0.053 mmol) in dry diethyl ether (20 ml) was added dropwise to lithium aluminium hydride (0.053 g; 1.5 mmol) in dry diethyl ether (30 ml) under hydrogen. The mixture was heated at reflux under nitrogen for 12 h. Diethyl ether saturated with water was added carefully. After complete destruction of the excess reducing agent, the solution was dried and filtered through celite. The solvent was removed under vacuum to give (5) as a yellow oil (0.1 g, 91%). MS m/z 128, 43, 32, 28* No molecular ion was observed. NMR data are summarised in table 4.

2-Methyl-5,6-benzo-2-azabicyclo[2.2.2]octane (6)[33]

The lactam (8) (0.92 g; 4.9 mmol) in dry diethyl ether (50 ml) was reduced with lithium aluminium hydride (1.0 g; 26.0 mmol) in dry diethyl ether as described for (5). The product (6) was isolated as a pale yellow oil (0.776 g; 91 %); spectroscopic data matched those recorded earlier.[33] NMR data are in table 4.

2-Methyl-5,6-benzo-2-azabicyclo[2.2.2]oct-7-ene-3-one (7)[35]

Benzene diazonium carboxylate was prepared from 2-aminobenzoic acid (19.0 g; 0.139 mol), isoamyl nitrite (19.24 g; 0.164 mol) and trifluoroacetic acid (1 ml) as described in reference 19. The crystalline product was filtered off carefully, washed with cold toluene, and kept moist with toluene (*explosion hazard when dry*[19]) during transfer to a flask containing 1-methyl-2-pyridone (15.10 g; 0.139 mol) in dry dichloromethane (200 ml). The mixture was stirred overnight under nitrogen and poured into water (300 ml). The organic layer was separated, dried and the solvent removed under vacuum. A pure sample of (7) was isolated by chromatography on silica using diethyl ether/petrol (80:20), (2.55g; 10%). Recrystallisation from acetone gave a sample, m.p. 103-5°C (lit. m.p. 98-100 °C[18]). ^{1}HMR δ 7.5 (m, 2H), 7.01 (m, 2H), 6.85 (m, 2H) 5.00 (dd, J=1.0, 3.6 Hz, 1H), 4.60 (dd, J=1.0, 3.6 Hz, 1H), 2.83 (s, 3H); ^{13}C NMR δ 172.7 (C=O), 141.6 (C), 140.5 (C), 136.8 (CH), 135.8 (CH), 125.8 (CH), 125.5 (CH), 123.9 (CH), 121.8 (CH), 62.3 (CH), 55.5 (CH), 32.6 (CH_3).

2-Methyl-5,6-benzo-2-azabicyclo[2.2.2]octan-3-one (8)[35]

The lactam (7) (1.0 g; 5.4 mmol) was dissolved in diethyl ether (40 ml) and hydrogenated over Pd/C for 6 h. The catalyst was removed by filtration through celite and the solvent removed under vacuum to give the saturated lactam (0.92 g; 91 %). Recrystallisation from diethyl ether/acetone [50:50] gave colourless crystals of (8), m.p. 129-131 °C, (lit. m.p. 133-5 °C[34]). ^{1}H NMR δ 7.2 (m, 4H), 4.46 (t, J ≈ 2 Hz, 1H), 3.86 (t, J ≈ 2.5 Hz, 1H), 2.90 (s, 3H), 2.0-2.2 (m, 2H), 1.59 (m, 2H). ^{13}C NMR δ 173.7 (C=O), 139.7 (C), 139.0 (C), 127.3 (CH), 126.2 (CH), 124.0 (CH), 121.6 (CH), 60.1 (CH), 47.5 (CH), 31.6 (CH_3), 27.0 (CH_2), 23.0 (CH_2).

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