NMR study of stereoelectronic anomeric and homoanomeric effects on the axial and equatorial CH bonds in 1,3-diazacyclohexanes and 1,5-diazabicyclo[3.2.1]octanes

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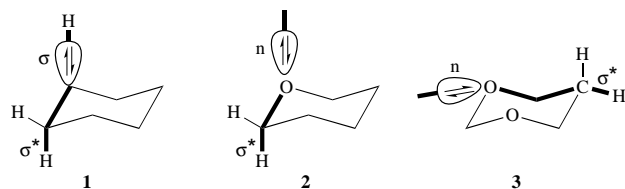*Chemistry Department, University College London, 20 Gordon Street, London, UK WC1H OAJ*

The ^{1}H and ^{13}C NMR spectra of a series of 1,3-di-*tert*-butyl-1,3-diazacyclohexanes **6**, and of 1,5-diaza-bicyclo[3.2.1]octanes **7**, have been investigated in an attempt to find evidence regarding a stereoelectronic interaction of the non-bonding electron pairs on nitrogen or of the C–N bonding electron pairs in the ring, with the axial and equatorial CH bonds of the α- or β-methylene groups. In **6**, the orbital carrying the non-bonding electron pair lies antiperiplanar to the axial α-CH bond; a significant $n_N{\to}\sigma^*_{CH}$ 3-orbital interaction (the anomeric effect) is sterically possible, and this shows up in the values of δ_H and of $^1J_{CH}$. In **7**, the doubly-occupied orbital is orientated *gauche* to both the axial and equatorial α-CH bonds, and no anomeric effect is apparent. In **7** however, in contrast to **6**, the stereochemistry is appropriate for a **W**-plan $n_N{\to}\sigma^*_{CH}$ 4-orbital interaction with the equatorial β-CH bond, and comparison of the NMR data of **6** and **7** suggests that such a homoanomeric effect may operate, though it is much weaker than in the analogous 1,3-dioxanes. No evidence could be found for a $\sigma_{CN}{\to}\sigma^*_{CH}$ 3-orbital interaction.

Introduction

The stereochemical nonequivalence of the axial and equatorial bonds in cyclohexanes in the chair conformation manifests itself in a number of ways, and is particularly evident in the NMR spectra. Typically, the chemical shift of the axial protons is 0.1–0.7 ppm upfield of that of the equatorial protons, $^3J_{H(ax)H(ax)}$ is 8–10 Hz, while $^3J_{H(ax)H(eq)}$ and $^3J_{H(eq)H(eq)}$ are 2–3 Hz, $^1J_{CH(ax)}$ is *ca.* 4 Hz less than $^1J_{CH(eq)}$, and $^4J_{H(eq)H(eq)} \geqslant 1$ Hz whereas $^4J_{H(eq)H(ax)} \ll 1$ Hz. This difference in the axial and equatorial one-bond coupling constants ($^1J_{CH(ax)} < ^1J_{CH(eq)}$) has been referred to as the Perlin effect,[1] and it has been suggested that it results from $\sigma_{CH}{\to}\sigma^*_{CH}$ 3-orbital† hyperconjugation which weakens the antiperiplanar axial CH bonds as illustrated in **1**. The corresponding $\sigma_{CC}{\to}\sigma^*_{CH}$ 3-orbital effect on $^1J_{CH(eq)}$ is assumed to be less.

Much attention has been paid to such effects in oxacyclo-hexanes partly because of the importance of these structures in carbohydrates. At the anomeric position in pairs of glycosides, $^1J_{CH(ax)}$ in the α-anomer is about 10 Hz less than $^1J_{CH(eq)}$ in the β-anomer.[1,2] This is one manifestation of the anomeric inter-action which particularly affects axial bonds in the α-position to the heteroatom compared with their equatorial counterparts. It is commonly ascribed to the $n_O{\to}\sigma^*_{CH}$ 3-orbital interaction of the axially directed lone pair on the oxygen with the σ^* orbital of the antiperiplanar axial CH bond as shown in **2**.[3] In contrast, the equatorial hydrogen is antiperiplanar to a bond in the ring skeleton.
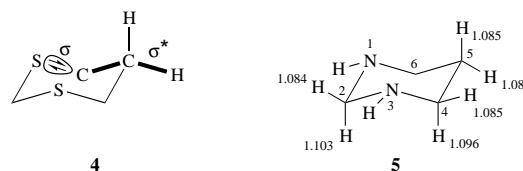
However, the NMR parameters are anomalous at the methyl-

ene groups in even the β-position to the oxygen. This was first recognised by Anteunis, Tavernier and Borremans,[4] who showed that at C-5 in 1,3-dioxanes, β-related to the two different oxygens, the axial protons are *less* shielded than the equatorial ones. We found an equivalent effect on the one-bond coupling constants at the 6-position in 1,2,4-trioxanes, where $^1J_{CH(ax)} > ^1J_{CH(eq)}$, *i.e.* the Perlin effect is reversed,[5] and in a series of 1,3-dioxanes and the related cyclic sulfites and dioxaphos-phorinanes,[6,7] $\delta(5\text{-H}_{ax}) < \delta(5\text{-H}_{eq})$, $^1J_{CH(ax)} > ^1J_{CH(eq)}$ and $^3J_{H(4eq)H(5ax)} > ^3J_{H(4ax)H(5eq)}$. It was suggested that this could be accounted for on the basis of a **W**-plan (extended antiperi-planar) through-space $n_O{\to}\sigma^*_{CH}$ 4-orbital homoanomeric interaction between the equatorially directed doubly-filled orbital on oxygen and the equatorial C(5)–H bond as shown in **3**.

In 1,3-dithianes, however, $^1J_{CH(ax)} > ^1J_{CH(eq)}$ at *all* positions round the ring,[8–10] some of which do not have sulfur lone pairs in a **W**-arrangement, and from *ab initio* calculations it was suggested[1,10] that the dominant interaction now is $\sigma_{CS}{\to}\sigma^*_{CH}$ (3-orbital) as shown in **4**. The values of $^1J_{CH(ax)}$ and $^1J_{CH(eq)}$ at the 2, 4, 5 and 6 positions in 1,3-oxathianes are compatible with the presence of all three of the effects illustrated in **2**, **3** and **4**.[10]

In 1957, Bohlmann[11,12] observed from IR spectra that a nitrogen lone pair has the effect of weakening an antiperiplanar C–H bond, suggesting an $n_N{\to}\sigma^*_{CH}$ 3-orbital interaction equivalent to **2**. In the NMR spectra, the equivalent effect shows up as a normal anomeric effect in aziridines, imidazol-idines,[13] oxaziridines,[14] piperidines,[15] oximes, hydrazones and imines,[16] *i.e.* the value of ^1J of a CH bond antiperiplanar to the nitrogen lone pair is less than that synperiplanar to a lone pair.

1   **2**   **3**

4   **5**

Ab initio 6-31G** calculations by Juaristi *et al.*[10] on hexa-hydropyrimidine gave the bond lengths (Å) shown in **5**. These reproduce clearly the weakening of the axial C-H bonds at C-2,

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† To distinguish similar interactions which can operate over different distances we denote the number of orbitals, whether bonding, non-bonding, or antibonding, which are needed to describe the system (see Results and Discussion).

Table 1 ^{1}H NMR (δ) of 1,3-diazacyclohexanes

		2-H	4,6-H	5-H	CMe$_3$	Me
	9[a]	3.30, br s	2.51, t, J 5.6	1.63, quin, J 5.6	1.04 s	
		ax 2.45, d, $J \sim 9$	ax 1.97, t, J 11	1.53, br m	1.04 s	
		eq 4.05, d, $J \sim 9$	eq 2.97, d, J 11	1.60, br m		
	10	ax 2.42, d, J 8.49	ax 1.61, dd, J 10.7, 10.7	1.77, ttquin	1.05, s	0.79, d, J 6.5
		eq 4.11 dt, J 1.81, 8.54	eq 2.98 ddd, J 10.7, 4.1, 1.8			

[a] At room temperature in CDCl$_3$ (upper entry) and -80 °C in CD$_2$Cl$_2$–CS$_2$ (lower entry) (see text).

Table 2 ^{1}H NMR (δ) of 1,5-diazabicyclo[3.2.1]octanes

		8-H	2,4-H	3-H	6,7-H	Me
	11	ax 3.94, d,	2.72–3.13, m	ax 1.84, dtt	2.72–3.13, m	
		eq 3.24, d, J 10.5		eq 1.07, dm, J 14.4		
	12	ax 3.81, q, J 6.2	2.57–2.89, m	ax 1.57, dtt	2.57–2.89, m	0.73, d, J 6.2
				eq 0.76, dtt		
	13	ax 3.96, q, J 6.3	ax 2.61, dd, J 11.7, 13.8	ax 1.88, m	2.84–3.03, m	0.65, Me-3 d, J 6.5
			eq 2.84–3.03, m			1.00, Me-8 d, J 6.4
	14	ax 4.48, s	eq 2.64, dd J 5.9, 14.0	ax 1.99, m	3.09, m	0.44, d, J 6.5
			ax 2.71 dd J 11.5, 14.3		3.23, m	
	15	ax 4.36, q, J 6.4		ax 0.79, t, J 12.1	[a]	[b]
				eq 0.96, dd, J 4.2, 12.1		

Ar = 4-nitrophenyl δ 7.79, 2H, d, J 9.01; 8.25 2H, d, J 8.90. [a] 2.58–2.63, 2H, m including 4-H(ax); 2.70–2.76, 1H, m; 2.84–2.87, 1H, m; 2.99–3.02, 1H, m. [b] 4-Me 0.88, d, J 6.61. 2-Me(eq) 0.97, s. 2-Me(ax) 1.16, s. 8-Me 1.02, d, J 6.43.

**Table 3** ^{13}C NMR chemical shifts of 1,3-diazacyclohexanes

	C-2	C-4,6	C-5	CMe$_3$	CMe_3	Me
9	65.42	46.02	26.93	53.41	26.58	
10	64.64	53.42	30.37	53.20	26.33	17.38

6   **7**   **8**

C-4 and C-6. They observed that it would be interesting to verify experimentally the predicted reduced or reversed Perlin effect at C-5, and, if so, to establish whether a homoanomeric W-plan through-space $n_N \rightarrow \sigma^*_{CH}$ 4-orbital (*cf.* **3**) or antiperiplanar anomeric $\sigma_{CN} \rightarrow \sigma^*_{CH}$ 3-orbital (*cf.* **4**) interaction might be responsible.

We report here an investigation of the ^{1}H and ^{13}C NMR spectra of some diazacyclohexanes with a single fixed configuration, namely 1,3-di-*tert*-butyl-1,3-diazacyclohexane **6** (1,3-di-*tert*-butylhexahydropyrimidine) and 1,5-diazabicyclo[3.2.1]-octane **7**. In **6** the bulky *tert*-butyl groups are oriented equatorially,[17,18] leaving the axial non-bonding electron pairs in a position to affect the axial protons at positions 2, 4 and 6 by $n_N \rightarrow \sigma^*_{CH}$ 3-orbital electron donation, but no W-plan inter-action is possible with the equatorial proton at C-5. Conversely, in **7**, the unshared electron pairs on nitrogen are equatorially directed permitting a W-interaction with the C(5)–H(eq) bond, but precluding any strong $n_N \rightarrow \sigma^*_{CH}$ 3-orbital interaction with the adjacent axially- or equatorially-directed C–H bonds which are *gauche* to the n_N orbital. Both **6** and **7**, on the other hand, could take part in a $\sigma_{CN} \rightarrow \sigma^*_{CH}$ 3-orbital interaction as shown in **8**. We hoped thus to be able to identify the relative role of any $n_N \rightarrow \sigma^*_{CH}$ (4-orbital) and $\sigma_{CN} \rightarrow \sigma^*_{CH}$ (3-orbital) effects on β-methylene groups, as well as to obtain further evidence for the anomeric interaction at the α-methylene groups.

Results and discussion

Values of [1]J_{CH} were obtained by observation of the ^{13}C satellites in the ^{1}H spectra, or from the undecoupled ^{13}C spectra. The former method requires that both the weak satellites be located in a region of the spectrum that is clear of other signals, or the assumption, if only one satellite is observable, that the carbon isotope effect on ^{1}H is unimportant, but the identification of the
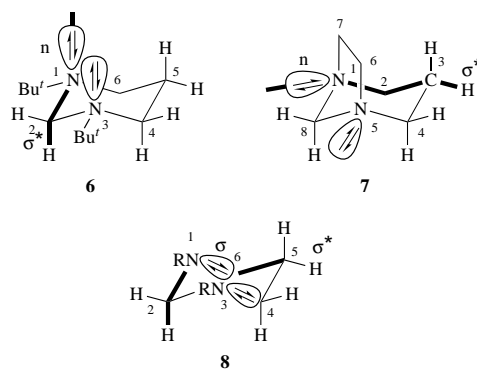
particular proton which is involved is usually unambiguous. The latter method is more generally applicable, but for a methylene carbon it may be difficult to assign the two one-bond couplings which are observed to the appropriate axial and equatorial protons.

Signals in the proton-coupled ^{13}C NMR spectrum are multiplets due to many two- and three-bond proton–carbon couplings. At low temperatures with additional line broadening, this may mean that it is impossible to separate two one-bond coupling constants of similar size.

To help solve these difficulties, ^{1}H spectra were recorded at both 400 and 200 MHz, and ^{13}C spectra at 100 and 50 MHz, and a variety of derivatives (**9–15**) of the basic structures **6** and **7** were studied. Details of the spectra are given in Tables 1–6. All the spectra were recorded in CDCl$_3$ solution at room temperature unless otherwise stated.

The nomenclature which we have used to describe the various interactions merits some discussion. In the term '$n_O \rightarrow \sigma^*$ anti-periplanar 3-orbital interaction', the '3-orbital' term refers to the lone pair and the two σ-bonding orbitals which define the structure of the molecular fragment, without implying that the interaction takes place through these two orbitals. In fact, it is usually accepted that the middle orbital plays no role in the transmission of the effect, which is the result of a through-space interaction of the frontal lobe of the lone pair and the antibonding third orbital. These interacting orbitals are not

Table 4 ^{13}C NMR chemical shifts of 1,5-diazabicyclo[3.2.1]octanes

	C-8	C-2,4	C-3	C-6,7	Me	Others
11	77.78	54.14	19.28	51.66		
12	84.16	55.75	17.50	49.32	18.28	
13	84.20	63.97	22.57	49.89	18.10 16.33	
14	82.58	54.17	23.74	53.39	16.48	123.89 127.61 129.83 123.5
15	77.92	55.42 54.81	36.18	41.51 44.21	18.39 20.46 27.41 30.22	

Table 5 One-bond coupling constants, $^{1}J_{CH}$/Hz, in 1,3-diazacyclohexanes

	C-2	C-4,6	C-5	CMe_3	Me
9	137.1 (av)	132.0 (av)	127.4 (av)	125.1	
10	ax 133.7 eq 142.1	ax 128.0 eq 138.8	ax 125.2	125.2	124.8

**Table 6** One-bond coupling constants, $^{1}J_{CH}$/Hz, in 1,5-diazabicyclo[3.2.1]octanes

	C-8	C-2,4	C-3	C-6,7	Me
12	145.3	137.4	ax 125.2 eq 127.4	141.4	125.8
13	149.2	136.5	ax 125.8	141.6	125.9 Me-8 125.3 Me-3
14	147.8	136.2	ax 125.2	142.4	125.0
15	146.4	132.1	ax 125 eq 125	135.4 138.0 144.1 143.7	125.9 Me-2 125.1 125.9 125.1

antiperiplanar, but *cis* 'eclipsed', but the effect is seen in the NMR parameters and other properties of the atoms of the antiperiplanar bond. The three orbital arrangement might be described as Z-plan instead of antiperiplanar. All these points are included in the term 'anomeric interaction'.

In the corresponding term '$n_O \rightarrow \sigma^*$ W-plan 4-orbital interaction', the '4-orbitals' are the lone pair and three σ-bonding orbitals, the middle two serving only to connect structurally the fourth which once again forms the bond which shows the effect of the interaction. The four orbitals are arranged in an 'extended antiperiplanar' arrangement which is conveniently called W-plan, but the interaction is not believed to take place through these orbitals. The interaction is envisaged between the backside of the lone pair orbital and the σ* antibonding orbitals which are both directed towards the middle of the 6-membered ring. All these points are implied by the term 'homoanomeric interaction'.

1,3-Di-*tert*-butyl-5-methyl-1,3-diazacyclohexane 10
Only the conformation shown in **10** is significantly populated at

9   **10**
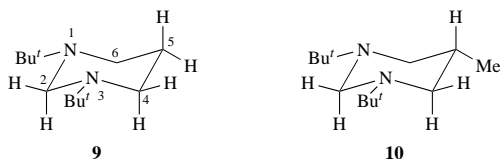
room temperature,[17,18] as indicated by the coupling constant of the proton in the 5-position, and separate signals for the axial and equatorial protons were observed. The 2-H_{eq} and 4,6-H_{eq} protons were identified from their mutual W-plan 4-bond coupling of 1.5 Hz. (Anteunis[4] observed a similar W-plan coupling of *ca.* 1.3 Hz in a series of conformationally rigid 1,3-dioxanes.) The axial protons at these positions are thus firmly identified (see Table 1) and show the usual $n_N \rightarrow \sigma^*_{CH}$ (3-orbital)

shielding by the antiperiplanar directed nonbonding electron pairs on nitrogen.

The values for $^{1}J_{CH}$ at H-2(ax), H-2(eq) and H-4,6(eq) were measured unambiguously from the ^{1}H NMR spectrum to be *ca.* 135, 141 and 138 Hz respectively, and, with these assignments, accurate values were obtained from the undecoupled ^{13}C NMR spectrum of $^{1}J_{CH-2(ax)}$ 133.7, $^{1}J_{CH-2(eq)}$ 142.1 Hz, $^{1}J_{CH-4,6(ax)}$ 128.0 and $^{1}J_{CH-46(eq)}$ 138.8 Hz. We assume that the axial bonds are weakened by the population of the σ^*_{CH} orbital by $n_N \rightarrow \sigma^*_{CH}$ hyperconjugation. At C-5, $^{1}J_{CH(ax)}$ was determined to be 125.2 Hz. If it is assumed that a similar value holds in 1,3-di-*tert*-butyl-1,3-diazacyclohexane **9** (see below), this allows the values in that compound to be assigned to $^{1}J_{CH(5ax)}$ and $^{1}J_{CH(5eq)}$.

1,3-Di-*tert*-butyl-1,3-diazacyclohexane 9
At room temperature the 400 MHz ^{1}H NMR spectrum shows a quintet for the 5-H protons, and broad singlets for the 2-H and 4,6-H protons; at 200 MHz, 5-H appears as a quintet, and 4,6-H as a triplet, with ^{3}J 5.6 Hz, but 2-H still shows a broad singlet (Table 1). Under these conditions, rapid inversion of the ring, and at the nitrogen centres, renders magnetically equivalent the geminal protons within each methylene pair, and averaged chemical shifts and coupling constants are being observed, but the signal-broadening indicates that dynamic effects are imminent.

At -80 °C, separate signals for the axial and equatorial protons are observed (at 400 MHz) as given in Table 1; the lines are broad, and smaller coupling constants than those quoted were apparent but were not well resolved. The signals for 2-H(ax) and H-2(eq) could be assigned following Katritzky[19,20] on the basis of the anomeric effect which had been observed with other nitrogen compounds,[13,15,16] and this assignment is confirmed by the observation of W-plan coupling in 5-methyl-1,3-di-*tert*-butyl-1,3-diazacyclohexane **10** between 2-H(eq) and 4,6-H(eq), as described above. The assignment of the signals for H-4,6(ax) [and thence H-4,6(eq)] was made from a large $^{3}J_{H(ax)H(ax)}$ coupling of *ca.* 11 Hz, and this is corroborated by the anomeric effect on chemical shifts. The H-5(ax) and H-5(eq) protons showed broad overlapping multiplets centred at δ 1.60 and 1.53. The larger width of the signal at δ 1.60 suggested that it should be ascribed to H-5(ax), but the resolution unfortunately was not good enough to permit any further firm conclusions to be drawn.

The signals for the non-equivalent geminal pairs of 4-H protons which were distinct at low temperature (Δδ 640 Hz), coalesced at 233 K, whence the rate constant of the interconversion of equivalent chair conformations by inversion of the ring and of the nitrogen atom configurations, between ground states with diequatorial *tert*-butyl groups, is calculated to be 2.84×10^3 s^{-1}, and $\Delta G^{\ddagger} = 10.2$ kcal mol^{-1} (1 cal = 4.184 J).[21] For 1,3-dimethyl-1,3-diazacyclohexane, for which there is about 10% of the ax,eq isomer at 123 K, Katritzky found (from ^{13}C NMR) that $\Delta G^{\ddagger}$ for inversion at nitrogen was *ca.* 7 kcal mol^{-1}, and for ring inversion was *ca.* 10 kcal mol^{-1}.[22] In **9**, with larger *tert*-butyl substituents, it seems likely that the inversion of the ring and at the nitrogen atoms [eqn. (1)] occurs as a coupled process which is unlikely to involve an intermediate with adjacent axial *N-tert*-butyl groups.
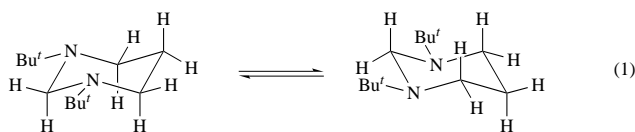
The undecoupled ^{13}C NMR spectra at 100.6 MHz for the ring carbon atoms showed time-averaged equal one-bond coupling to the pairs of methylene protons down to −80 °C (Table 5), although the triplet due to ^1J coupling should change to a doublet of doublets at lowest temperatures when H_{ax} and H_{eq} are distinct on the NMR timescale. These average values for coupling at C-1 and C-4,6 are close to the mean of the explicitly measured values of $^1J_{CH(ax)}$ and $^1J_{CH(eq)}$ in 1,3-di-*tert*-butyl-5-methyl-1,3-diazacyclohexane **10** (see above). This suggests that at C-2 in di-*tert*-butyl-1,3-diazacyclohexane, $^1J_{CH(ax)} = ca.$ 133.9 and $^1J_{CH(eq)} = ca.$ 141.3 Hz.

At C-5, the average of $^1J_{CH(ax)}$ and $^1J_{CH(eq)}$ was 127.4 Hz, and on the basis of the value of *ca.* 125.2 Hz for $^1J_{CH(ax)}$ as reported above for **10**, the values of $^1J_{CH-5(ax)}$ and $^1J_{CH-5(eq)}$ in 1,3-di-*tert*-butyl-1,3-diazacyclohexane can be estimated to be about 125.2 and 129.6 Hz respectively, *i.e.* that there is a normal Perlin effect ($^1J_{CH-5(ax)} - ^1J_{CH-5(eq)} = −4.4$ Hz) of a similar magnitude to that in cyclohexane ($^1J_{CH-5(ax)} - ^1J_{CH-5(eq)} = −4.0$ Hz) which may be seen as resulting from the $\sigma_{C(4,6)H(ax)} \rightarrow \sigma^*_{CH}$ interaction. Such coupling constants offer no evidence in this system of significant $n_N \rightarrow \sigma^*_{CH}$ 4-orbital interaction with CH-5(eq) and such an interaction with CH-5(ax) is unlikely for the stereochemistry is wrong. Likewise there is no need to invoke the sterically possible $\sigma_{CN} \rightarrow \sigma^*_{CH}$ 3-orbital interaction.

1,5-Diazabicyclo[3.2.1]octanes 11–15
In the 1,5-diazabicyclo[3.2.1]octanes with equatorial nitrogen lone pairs in the 6-membered ring, interpretation of the ^{1}H NMR spectra was sometimes complicated by overlap of the signals of the CH_2CH_2 bridge with those of the methylene groups at the 2- and 4-positions, but methylation at C-3 aids in the interpretation. In 3,8-dimethyl-1,5-diazabicyclo[3.2.1]octane **13**, the signal for H-2,4(ax) stands out clearly as a doublet of doublets at δ 2.61 with $J_{H,H}$ 11.7 and 13.8 Hz, slightly *upfield* of the signal for H-2,4(eq) which lies between δ 2.84 and 3.03, overlapping the protons of the ethylene bridge. In contrast, in 8-*p*-nitrophenyl-3-methyl-1,5-diazabicyclo[3.2.1]octane **14**, H-2,4(ax) stands out similarly as a doublet of doublets, $J_{H,H}$ 11.5 and 14.3 Hz, just downfield of H-2,4(eq) with $J_{H,H}$ 14.1 and 5.9 Hz. In these compounds the doubly-occupied non-bonding orbital on nitrogen with approximately sp³ hybridisation, lies *gauche* with respect to both the C(2,4)-H(ax) and
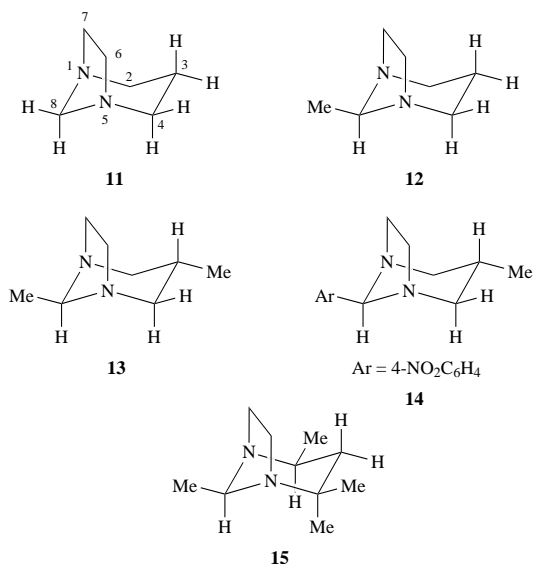
C(2,4)-H(eq) bonds. Any $n \rightarrow \sigma^*_{CH}$ 3-orbital interaction is of similar magnitude with both protons, and has a similar effect on their chemical shifts which are therefore sensitive to other small substituent shielding effects.

Alder *et al.*[23] showed that the equatorial proton at C-8 in 1,5-diazabicyclo[3.2.1]octane **11** can be identified at δ 3.24 as it shows long-range W-plan coupling to the equatorial protons at C-2 and C-4: 8-H(ax) appears at δ 3.94. This relative chemical shift is greater than that for the methylene groups at C-2 and C-4, but still much less than for the corresponding two C-2 protons in the diazacyclohexanes **9** and **10**. Again this can be ascribed to the fact the sp³ orbital on nitrogen which contains the non-bonding electron pair lies near-*gauche* to both CH bonds at C-8, and affects both similarly.

Values of $^1J_{CH}$ for the axial C(3)-H bond in 3,8-dimethyl-1,5-diazabicyclo[3.2.1]octane **13** and 3-methyl-8-*p*-nitrophenyl-1,5-diazabicyclo[3.2.1]octane **14**, were found to be 125.8 and 125.2 Hz respectively (close to the value of 125.2 Hz found for the equivalent bond in 1,3-di-*tert*-butyl-5-methyl-1,3-diazacyclohexane, **10**). For 8-methyl-1,5-diazabicyclo[3.2.1]octane **12** the values measured for the CH_2 group at the 3-position were 125.2 and 127.4 Hz. It seems reasonable then to conclude that these two figures correspond to the axial and equatorial C–H couplings respectively.

In the undecoupled ^{13}C spectrum of **15**, the signal for C-3 is much broadened by additional small couplings to methyl protons and appears as a triplet with the width of the central line equal to that of the other two, implying that $^1J_{CH(ax)}$ is not detectably different from $^1J_{CH(eq)}$ with a value of about 125 Hz.

This difference of 2.2 Hz in one-bond coupling constants in **12** is about half that in 1,3-di-*tert*-butyl-1,3-diazacyclohexane (see above) or cyclohexane, and the results with **15** are consonant with this. A plausible rationalisation is that there is an $n_N \rightarrow \sigma^*_{CH}$ 4-orbital interaction to the β position, which is dependent on the orientation of the n_N orbital, but even when it is stereochemically favourable (*i.e.* for the equatorial proton), it is only half the size of the opposing $\sigma_{CH} \rightarrow \sigma^*_{CH}$ 3-orbital interactions from the two α-methylene groups, and much smaller than that of the two oxygen atoms in 1,3-dioxanes which have the effect (perhaps by $n_O \rightarrow \sigma^*_{CH}$ 4-orbital interaction) of changing the value of $^1J_{CH-5(ax)} - ^1J_{CH-5(eq)}$ of −4.0 Hz in cyclohexane into *ca.* +6 Hz in the dioxanes.

Conclusion

We conclude that in the dioxa-[7] and trioxa-cyclohexanes,[5,6] the NMR spectra show evidence of both a $\sigma_O \rightarrow \sigma^*_{CH}$ (3-orbital) and $\sigma_O \rightarrow \sigma^*_{CH}$ (4-orbital) interaction. In the corresponding sulfur compounds, the results can be accomodated by a $\sigma_{CS} \rightarrow \sigma^*_{CH}$ (3-orbital) effect.[1,10] The 1,3-diazacyclohexanes and 1,5-diazabicyclo[3.2.1]octanes which we have investigated support the existence of a $\sigma_N \rightarrow \sigma^*_{CH}$ (3-orbital) (anomeric effect). There is some evidence for a weak $\sigma_N \rightarrow \sigma^*_{CH}$ (4-orbital) interaction, but none for a $\sigma_{CN} \rightarrow \sigma^*_{CH}$ (3-orbital) interaction.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on CDCl₃ solutions on a Varian XL200 or VXR-400 spectrometer, chemical shifts being measured relative to the solvent (δ_H 7.24 and δ_C 77.00); coupling constants are in Hz. IR spectra were recorded on a Perkin-Elmer PE 983 instrument, and mass spectra on a VG 7070H instrument, with electron ionisation. Column chromatography was carried out on Merck silica gel 60 (70–230 mesh).

1,3-Di-*tert*-butyl-1,3-diazacyclohexane 9.[19,24] Formaldehyde gas from paraformaldehyde (5 g) was passed through a stirred solution of *N,N′*-di-*tert*-butylpropane-1,3-diamine[25] (1.0 g) in diethyl ether (40 cm³) containing K₂CO₃ (10 g). The solvent was evaporated from the filtered solution and the product (90%

11

12

13

Ar = 4-NO₂C₆H₄

14

15

yield) was isolated by chromatography using 10:1 diethyl ether–light petroleum (bp 30–40 °C) as eluent. *m/z* 198 (M$^+$, 21%), 197 (M − 1, 100), 183 (M − Me, 6), 141 (M − Bu^t, 14), 127 (42), 98 (Bu^{t}N=CH−N$^+$, 30).

5-Methyl-1,3-di-*tert*-butyl-1,3-diazacyclohexane 10. 2-Methyl-1,3-dibromopropane was heated with *tert*-butylamine in water at 60 °C for 13 h, giving 2-methyl-*N*,*N*′-di-*tert*-butylpropane-1,3-diamine (7% yield), mp 54–56 °C, δ_H 0.88 (3H, d, *J* 6.8, Me), 1.04 (18H, s, Bu^t), 1.61 (1H, m, CH), 2.45 (4H, d, *J* 6.77).

This was treated with formaldehyde as above, giving **10** (90% yield). *m/z* 212 (M$^+$, 15%), 211 (M − H, 100), 197 (M − CH$_3$, 12), 155 (M − Bu^t, 10), 141 (18), 126 (8), 112 (18), 99 (72), 84 (18), 57 (Bu^t, 67). HRMS 212.2230. C$_{13}$H$_{28}$N$_2$ requires 212.2252.

1,5-Diazabicyclo[3.2.1]octane 11. Formaldehyde gas, from paraformaldehyde (5 g) was passed through a stirred solution of 1,4-diazacycloheptane (4 g) in CH$_2$Cl$_2$ (40 cm^3) containing K$_2$CO$_3$ (5 g), yielding **11** as a solid which was recrystallised from pentane; mp 106–108 °C, 35% yield. *m/z* 112 (M$^+$, 38%), 84 (25), 70 (12), 57 (100), 42 (93). HRMS 112.1012. C$_6$H$_{12}$N$_2$ requires 112.1001.

8-Methyl-1,5-diazabicyclo[3.2.1]octane 12. A mixture of 1,4-diazacycloheptane (3 g), acetaldehyde (excess, freshly distilled), and anhydrous MgSO$_4$ (10 g) in diethyl ether (30 cm^3) was stirred for 3 h. The solution was filtered and distilled yielding **12**, (85%), bp 65–67 °C/16 mmHg. *m/z* 126 (M$^+$, 100%), 83 (44), 71 (64). HRMS 126.1162; C$_7$H$_{14}$N$_2$ requires 126.1157.

3-Methyl-8-(4-nitrophenyl)-1,5-diazabicyclo[3.2.1]octane 14. Methacrolein (7.2 g) was added dropwise to ethylenediamine (6.0 g) in methanol (20 cm^3), and stirred for 2 h, keeping the temperature below 0 °C throughout. A buffer solution from NaOAc (16.1 g), HOAc (84.0 cm^3) and water (156 cm^3) was added, the mixture was cooled to 0 °C, and NaBH$_4$ (16.0 g) was added slowly with stirring. 6-Methyl-1,4-diazacycloheptane was isolated (20%) yield, bp 69–70 °C/16 mmHg (lit.,[26] 181–181.3 °C/755 mmHg). δ_H 0.80 (3H, d, *J* 6.84, Me), 1.64 (2H, bd, NH), 1.71 (1H, m, CH), 2.41 (2H, dd, *J* 8.43, 13.68, CH$_2$-5,7), 2.85 (4H, m, CH$_2$CH$_2$), 3.00 (2H, dd, *J* 4.97, 13.65, CH$_2$-5,7).

This diazepine (0.57 g), 4-nitrobenzaldehyde (0.75 g), and MgSO$_4$ (10 g) in CH$_2$Cl$_2$ (40 cm^3) were heated under reflux for 30 min. The product was isolated by filtration and distillation, and recrystallised from pentane/diethyl ether (5:1) giving **14** (30% yield), mp 145–146 °C. Found: C, 63.2; H, 6.9; N, 17.0. C$_{13}$H$_{17}$N$_3$O$_2$ requires C, 63.14; H, 6.93; N, 16.99%.

2,2,4,8-Tetramethyl-1,5-diazabicyclo[3.2.1]octane 15. 5,5,7-Trimethyl-1,4-diazacycloheptane[27] was treated with acetaldehyde as above to give **15**, (90% yield), bp 86–88 °C/17 mmHg. *m/z* 168 (M$^+$, 27%), 153 (M − Me, 13), 140 (12), 126 (20), 112 (19), 98 (18), 83 (58), 70 (88), 56 (100). HRMS, 168.1630; C$_{10}$H$_{20}$N$_2$ requires 168.1626. Found: C, 71.1; H, 11.8; N, 16.6. C$_{10}$H$_{20}$N$_2$ requires C, 71.36; H, 11.99; N, 16.65%.

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