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Hydroacridines XX [1]. Stereochemical Factors Influencing the ^{13}C NMR Protonation Shifts of Six-membered Saturated Azaheterocyclic Tertiary Amines

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Summary. The influence of stereochemical factors upon ^{13}C NMR shifts induced by N-protonation of saturated azaheterocyclic tertiary amines was investigated using (4aα,8aβ,9aβ,10aα)-tetradecahydro-10-methylacridine, (4aα,8aβ,9aβ,10aα)-10-ethyl-tetradecahydroacridine, (4aα,8aα,9aβ,10aα)-tetradecahydro-10-methylacridine, and (4aα,8aα,9aβ,10aα)-10-ethyl-tetradecahydroacridine as model compounds. The magnitudes of the protonation shifts depend on the following stereochemical factors: (*i*) whether protonation occurs through an axial or an equatorial nitrogen electron lone-pair, (*ii*) the relative steric orientation (γ-*gauche* or γ-*anti*) of the nitrogen and carbon atoms in γ position, and (*iii*) the geometry of the entire carbon skeleton. Similar stereochemical dependences were found for the protonation shifts on N-methyl-*trans*-decahydroquinoline, analyzed on the basis of chemical shift data from literature. The observed protonation shifts can be well rationalized in terms of the LEFS (linear electric field shift) theory.

Keywords. Acridines, tetradecahydro; Quinolines, decahydro; ^{13}C NMR; Protonation shifts; Solvent effects.

Hydroacridine, 20. Mitt. [1]**. Stereochemische Faktoren, die die durch Protonierung induzierten ^{13}C-NMR-Verschiebungen von sechsgliedrigen gesättigten azaheterozyklischen tertiären Aminen beeinflussen**

Zusammenfassung. Der Einfluß stereochemischer Faktoren auf die durch N-Protonierung von sechsgliedrigen gesättigten azaheterozyklischen tertiären Aminen hervorgerufenen ^{13}C-NMR-Verschiebungen wurde anhand von (4aα,8aβ,9aβ,10aα)-Tetradecahydro-10-methylacridin, (4aα,8aβ,9aβ,10aα)-10-Ethyl-tetradecahydroacridin, (4aα,8aα,9aβ,10aα)-Tetradecahydro-10-methylacridin und (4aα,8aα,9aβ,10aα)-10-Ethyl-tetradecahydroacridin als Modellverbindungen untersucht. Die Größe der ^{13}C-Protonierungsshifts ist von folgenden stereochemischen Faktoren abhängig: (*i*) der Protonierung über ein axiales oder ein äquatoriales unbeteiligtes Elektronenpaar des Stickstoffatoms, (*ii*) des relativen sterischen Verhältnisses (γ-*gauche* oder γ-*anti*) zwischen dem Stickstoffatom und den in γ-Stellung befindlichen Kohlenstoffatomen und (*iii*) der Geometrie des gesamten Kohlenstoffgerüsts. Gleiche stereochemische Abhängigkeiten werden für die Protonier-

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ungsverschiebungen von N-Methyl-*trans*-decahydroquinolin gefunden, die auf der Basis von Literaturdaten untersucht wurden. Die beobachteten Protonierungsverschiebungen können mittels der Theorie der linearen elektrischen Feldverschiebung (LEFS) gut erklärt werden.

Introduction

The change in chemical shifts induced by protonation ($\delta_{\text{protonated form}}-\delta_{\text{free base}}$) has been defined as protonation shift [2, 3]. This definition, however, is correct only provided that protonated forms exhibit no stereochemical change with respect to the free base; otherwise, the observed chemical shift difference is a result of the combined effects of both protonation and geometry change, and only in a few cases the individual contributions can be separated. Studies on the ^{13}C NMR protonation shifts of saturated amines have been performed to allow a better rationalization of the ^{13}C NMR shifts caused by protonation of amino acids, peptides, and antibiotics which possess amino functionalities ([3–6] and references therein). As shown previously [2–9], the directions and magnitudes of the ^{13}C protonation shifts of saturated amines are controlled by various structural factors (*e.g.* the number of bonds separating the amino nitrogen and the carbon of interest, the degree of substitution at the amino nitrogen and at carbon atoms, the molecular conformation, *etc*.). For acyclic amines, owing to a large amount of experimental data (over 70 compounds have been investigated [3, 5, 6]), empirical correlation of protonation shifts with structural features has achieved considerable progress, allowing satisfactory quantitative predictions of protonation shifts for these compounds. Nevertheless, because of the marked solvent dependence of the observed protonation shifts, rather large discrepancies between the magnitudes of specific protonation shifts occur in the literature (see Table 1 and the corresponding discussion). By the LEFS (linear electric field shift) theory of *Batchelor* [4–6], a good rationalization of the observed shifts became also possible.

For saturated azaheterocyclic amines, however, very little experimental data are available, and the contributions of certain important stereochemical factors are yet controversial. On the basis of experimental data and of CNDO/MO calculations, *Morishima et al*. [2] concluded that protonation shifts (especially for carbons in β position) depend on the steric orientation of the nitrogen lone-pair electrons being protonated, in connection with the geometry (zigzag or folded) of the transmission path of the charge redistribution. The validity of their interpretation, however, has been strongly questioned by *Eliel* and *Vierhapper* who have studied some features of protonation shifts of *trans*-decahydroquinolines [8]. In the following we give two additional arguments why at least the experimental values in Ref. [2] are questionable. First, the group of *Morishima* compared the protonation shifts of β-carbons in quinuclidine and N-H piperidines (which they allegedly considered as model compounds for equatorial protonation through a zigzag transmission path) with those of β-carbons in quinolizindine and N-methylpiperidines (as model compounds for axial protonation through a folded transmission path). The data of the present paper and of others [5–7], however, show that comparisons between protonation shifts in different compounds cannot be conclusive, as any change in the structural formula, even not affecting the transmission path, can induce considerable changes of protonation shifts. Second, the magnitudes of protonation

Table 1. Solvent dependence of the protonation shifts of saturated amines

	Observed protonation shift[a]				Anion	Solvent	Ref.
	C-1	C-2	C-3	C-4			
n-Butyl	−1.47	−6.23	−0.75	−0.47	Cl^-	[b]	[3]
	−2.08	−6.72	−0.23	−0.41	Cl^-	[c]	[3]
	−2.8	−6.9	−0.8	−1.3	CF_3COO^-	[d]	[2]
Cyclohexyl	+0.68	−5.52	−1.19	−1.31	Cl^-	[b]	[3]
	+0.5	−5.7	−0.9	−1.1	Cl^-	[c]	[3]
	+0.78	−5.16	−1.00	−1.08	Cl^-	[e]	[7]
	+2.7	−6.1	−1.2	−1.8	CF_3COO^-	[d]	[2]
1-Adamantane	+5.48	−4.82	−0.76	−1.04	Cl^-	[e]	[6]
	+5.8	−5.5	−0.3	−0.6	f	[g]	[10]
	+8.2	−5.3	−0.6	−1.6	CF_3COO^-	[h]	[2]

[a] Shift values in ppm; the minus and plus signs mean upfield and downfield protonation shifts, respectively; [b] both free base and protonated form in D_2O; [c] both free base and protonated form in $CDCl_3$; [d] free base neat, protonated form in $CDCl_3$; [e] both free base and protonated form in D_2O-dioxane (3:1); [f] not specified; [g] protonation shifts deduced from reported chemical shifts (Ref. [10]) for the free base in $CDCl_3$ and for the protonated form in D_2O; [h] free base in $CDCl_3$, protonated form in CF_3COOH

shifts measured and considered in Ref. [2] are unreliable because the ^{13}C chemical shifts of the free amines have been measured as neat liquid (for two solid compounds in $CDCl_3$ solution), whereas those of the corresponding protonated species have been measured in trifluoroacetic acid solution. For comparison, the protonation shift values for three different amines as determined in Ref. [2] and by others are listed in Table 1. The large discrepancies (especially for carbons C-1 in α position) demonstrate the importance of measuring ^{13}C chemical shifts of both free amine and its protonated form in the same solvent. The effect of changing the solvent has already been emphasized for *trans*-decahydroquinolines [8]; however, it has been proven that the nature of the anion of the salt (Cl^- or CF_3COO^-) has no influence on protonation shifts if the amine and its salt are measured in the same solvent [8]. The most appropriate solvent to study protonation shifts of amines seems to be $CDCl_3$, because it well dissolves almost all amines and a great part of their salts, it does negligible protonate (due to the presence of unavoidable traces of acid) the free amines (*e.g.*, for the measurement of free amines in D_2O, the *pD* of the solutions has to be adjusted with alkaline hydroxide to suppress protonation [3, 5–7]), and internal *TMS* can be employed as reference.

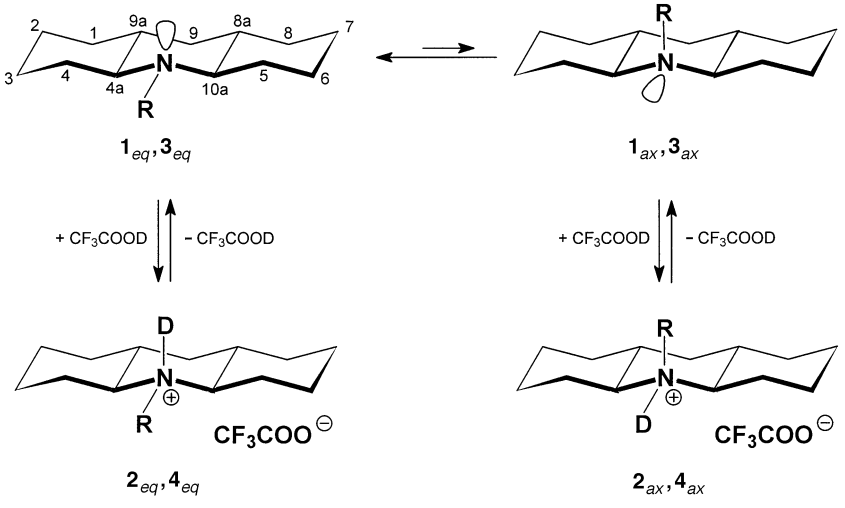
In the present work we have examined the ^{13}C NMR shifts of (4aα,8aβ,9aβ,10aα)-tetradecahydro-10-methylacridine (**1**), (4aα,8aβ,9aβ, 10aα)-10-ethyl-tetradecahydroacridine (**3**), (4aα,8aα,9aβ,10aα)-tetradecahydro-10-methylacridine (**5**), (4aα,8aα,9aβ,10aα)-10-ethyl-tetradecahydroacridine (**7**), and their deuterotrifluoroacetates $\mathbf{2}_{eq}$–$\mathbf{2}_{ax}$, $\mathbf{4}_{eq}$–$\mathbf{4}_{ax}$, **6**, and **8** (Schemes 1 and 2) in terms of possible influences of stereostructural factors on the ^{13}C protonation shifts of saturated six-membered azaheterocyclic tertiary amines. Owing to the conformational stability and well defined geometry of their tricyclic frameworks [11], amines **1**, **3**, **5**, and **7** are excellent model compounds for this kind of

stereochemical studies. In addition, with the aid of chemical shifts data from literature [8], certain stereochemical influences on the protonation shifts of N-methyl-*trans*-decahydroquinoline (**9**) were also examined.

Results and Discussion

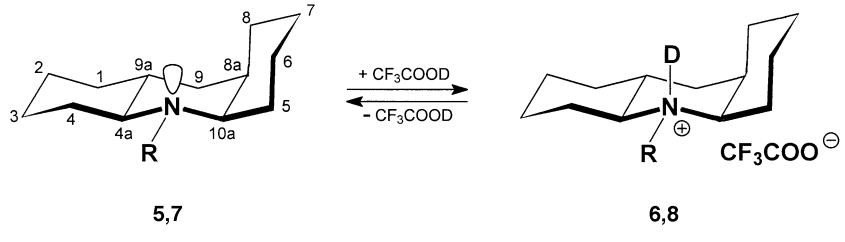
For the protonation of amines **1**, **3**, **5**, and **7**, actually deuterated trifluoroacetic acid was used and, hence, deuteronation shifts should be the correct term to be used. However, for convenience, within this paper we will use the usual term protonation shifts.

The isotope effect exerted by substituting hydrogen by deuterium on the ^{13}C NMR chemical shifts of the carbon atoms in α and β positions with respect to the aminic nitrogen in the salts (*i.e*, in β and γ positions, respectively, to deuterium) results mostly in upfield shifts of less than 0.2 ppm [12]. The isotope effect on more remote carbons should be expected to be within or below the limits of experimental error. Thus, as the shifts induced by deuteronation almost always surpass ± 1 ppm (see Table 2), no qualitative difference arises between protonation and deuteronation shifts.



$\mathbf{1}_{eq}, \mathbf{1}_{ax}, \mathbf{2}_{eq}, \mathbf{2}_{ax}$: *R* = Me; $\mathbf{3}_{eq}, \mathbf{3}_{ax}, \mathbf{4}_{eq}, \mathbf{4}_{ax}$: *R* = Et

Scheme 1



5,**6**: *R* = Me; **7**,**8**: *R* = Et

Scheme 2

Amines **1** and **3** undergo both axial and equatorial protonation, each giving rise to a pair of N-epimeric salts ($\mathbf{2}_{eq}$–$\mathbf{2}_{ax}$ and $\mathbf{4}_{eq}$–$\mathbf{4}_{ax}$, respectively; Scheme 1), whereas amines **5** and **7** undergo only axial protonation, providing the salts **6** and **8** (Scheme 2). The stereostructural and ^{13}C NMR signal assignments of compounds **1**–**8** (Table 2) and the quantitative parameters of the conformational equilibria of

Table 2. ^{13}C NMR chemical shifts and shift differences of amines **1**, **3**, **5**, **7**, and their deuterotrifluoroacetates $\mathbf{2}_{eq}$–$\mathbf{2}_{ax}$, $\mathbf{4}_{eq}$–$\mathbf{4}_{ax}$, **6**, and **8**, respectively (±0.1 ppm)[a]

	Compound									
	$\mathbf{1}=\mathbf{1}_{eq}$[b]	$\mathbf{2}_{eq}$	$\mathbf{2}_{ax}$	$\mathbf{3}=\mathbf{3}_{eq}$	$\mathbf{4}_{eq}$	$\mathbf{4}_{ax}$	**5**	**6**	**7**	**8**
C-1	33.46	32.41	32.46	33.26	32.31	32.01	33.71	32.29	33.66	32.33
		−1.05	−1.00		−0.95	−1.25		−1.42		−1.33
C-2	25.83	24.12	24.47	25.71	24.00	(24.29)	25.71	23.55	25.76	23.57
		−1.71	−1.36		−1.71	−1.42		−2.16		−2.19
C-3	26.10	24.95	24.71	25.98	24.81	(24.35)	26.07	24.63	26.09	24.51
		−1.15	−1.39		−1.17	−1.63		−1.44		−1.58
C-4	31.03	27.68	27.78	30.47	27.27	27.18	30.52	26.18	30.03	25.82
		−3.35	−3.25		−3.20	−3.29		−4.34		−4.21
C-4a	69.28	70.68	67.80	63.98	65.96	68.97	70.21	71.01	64.38	65.73
		1.40	−1.48		1.98	4.99		0.80		1.35
C-5	31.03	27.68	27.78	30.47	27.27	27.18	30.74	27.22	30.18	26.77
		−3.35	−3.25		−3.20	−3.29		−3.52		−3.41
C-6	26.10	24.95	24.71	25.98	24.81	(24.35)	19.74	17.72	20.40	18.04
		−1.15	−1.39		−1.17	−1.63		−2.02		−2.36
C-7	25.83	24.12	24.47	25.71	24.00	(24.29)	26.86	24.68	26.77	24.61
		−1.71	−1.36		−1.71	−1.42		−2.18		−2.16
C-8	33.46	32.41	32.46	33.26	32.31	32.01	27.37	24.98	27.02	24.86
		−1.05	−1.00		−0.95	−1.25		−2.39		−2.16
C-8a	40.99	39.00	32.56	41.37	38.90	33.04	37.55	34.89	37.47	34.69
		−1.99	−8.43		−2.47	−8.33		−2.66		−2.78
C-9	40.69	37.71	38.29	40.67	37.71	38.05	39.35	36.20	39.49	36.21
		−2.98	−2.40		−2.93	−2.59		−3.15		−3.18
C-9a	40.99	39.00	32.56	41.37	38.90	33.04	36.95	33.87	37.09	33.80
		−1.99	−8.43		−2.47	−8.33		−3.08		−3.29
C-10a	69.28	70.68	67.80	63.98	65.96	68.97	63.67	65.37	57.22	59.81
		1.40	−1.48		1.98	4.99		1.70		2.59
N–CH_3 eq	36.07	35.00	–	–	–	–	36.54	35.12	–	–
		−1.07						−1.42		
N–CH_3 ax	–	–	27.10	–	–	–	–	–		–
			−8.97							
N–CH_2 eq	–	–	–	38.95	40.32	–	–	–	38.44	39.68
					1.37					1.24
N–CH_2 ax	–	–	–	–	–	39.66	–	–	–	–
						0.71				
C–CH_3	–	–	–	7.22	5.53	13.82	–	–	5.40	4.42
					−1.69	6.60				−0.98

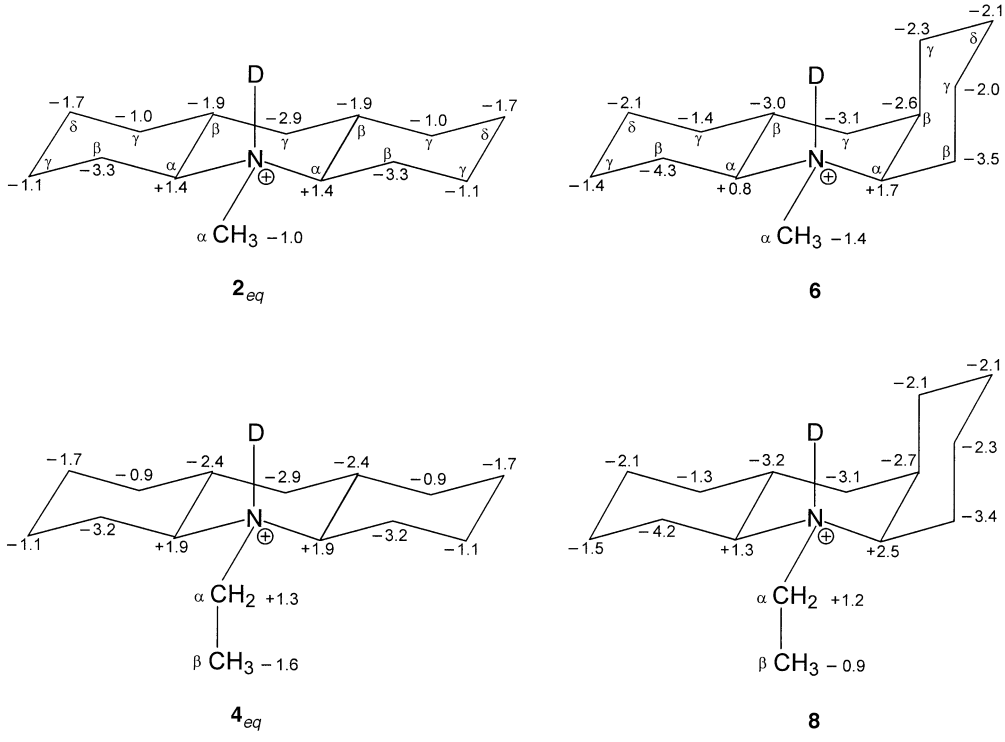
[a] In parts per million downfield from internal *TMS* in $CDCl_3$; the values in parentheses are ambiguous and may be interchanged; the figures in the second lines represent the shift differences between the protonated forms and their parent amines; [b] chemical shifts taken from Ref. [8]

the salts pairs $\mathbf{2}_{eq}$–$\mathbf{2}_{ax}$ and $\mathbf{4}_{eq}$–$\mathbf{4}_{ax}$ have already been discussed in the previous paper (part 19) of this series [1].

For the amines examined here, the protonation shifts of carbons located in various positions (α, to δ) with respect to the nitrogen atom generally exhibit the same trends in direction and magnitude as found for open-chain tertiary amines [3]. The tricyclic amines discussed here, however, allow to notice several effects caused by stereochemical factors which have not been present in the smaller amine molecules studied so far [2–9]; we wish to highlight these effects in the following discussion. In completion, on the basis of literature chemical shift data [8], these stereochemical effects, having not been considered in the original work [8], are shown to operate upon the protonation shifts of N-methyl-*trans*-decahydroquinoline (**9**), too.

Steric effects on protonation shifts of carbons in α position

Most incitative was to check whether there is any difference between shifts induced in one and the same amine by protonation through an axial nitrogen electron lone-pair or an equatorial lone-pair, respectively. The axial protonation shifts (APS) are simply given by the chemical shift differences between compounds $\mathbf{2}_{eq}$–$\mathbf{1}_{eq}$, $\mathbf{4}_{eq}$–$\mathbf{3}_{eq}$, **6**–**5**, and **8**–**7** (see Table 2). An optimal survey of the APS of these compounds is provided by Scheme 3.



Scheme 3. ^{13}C NMR shifts induced by axial N-protonation of amines **1**, **3**, **5**, and **7** to yield the salts $\mathbf{2}_{eq}$, $\mathbf{4}_{eq}$, **6**, and **8**, respectively (shift values in ppm, negative signs mean upfield)

According to investigations on C,N-dimethyldecahydroquinolines [8] sterically related with our amines, for amine **1** the portion of conformer $\mathbf{1}_{eq}$ should be at least 95%, and for amine **5** the portion of equatorial N–CH_3 even 100%. Hence, the contribution of conformation $\mathbf{1}_{ax}$ may be neglected, and the averaged spectrum of **1** may be considered as practically identical with the spectrum of $\mathbf{1}_{eq}$. Moreover, the spectra of amines **3**, **5**, and **7** correspond to their equatorial N-alkyl conformers.

The changes in chemical shifts observed upon transformation of amines **1** and **3** in the products of equatorial protonation $\mathbf{2}_{ax}$ and $\mathbf{4}_{ax}$, respectively, obviously are not the true equatorial protonation shifts (TEPS) but effective equatorial protonation shifts resulting from a combination of both the effects of equatorial protonation and of changing the steric orientation of the N-alkyl group with respect to the parent amine. Nevertheless, at least for the transformation of **1** into $\mathbf{2}_{ax}$ the following approach to separate the contribution of N-protonation is possible: The effects of introduction of an equatorial and of an axial N-methyl group, respectively, on the ring carbon shifts in *trans*-decahydroquinoline have been established earlier [8]; owing to their structural relationship and to the close similarity between the chemical shifts of appropriate carbons in *trans*-decahydroquinoline [8] and *trans-cisoid-trans*-tetradecahydroacridine [8, 11], one may expect the effects of N-methyl groups in *trans*-decahydroquinoline to be valid for appropriate carbons of *trans-cisoid-trans*-tetradecahydroacridine as well. As this hypothesis indeed holds very well for the chemical shifts of C-4a/10a in $\mathbf{1}_{eq}$[a], one may reasonably assume that no sizeable error should be expected for the axial N-methyl conformer $\mathbf{1}_{ax}$ as well. Thus, on adding 3 ± 0.2 ppm (the effect of an axial N-methyl group upon the chemical shift of C-8a in *trans*-decahydroquinoline [8]) to 61.83 ppm (see footnote[a]) we obtain 64.83 ± 0.2 ppm as the predicted chemical shift of C-4a/10a in $\mathbf{1}_{ax}$. On subtracting this from 67.80 ppm (the observed value for the corresponding salt $\mathbf{2}_{ax}$), a downfield shift of 2.97 ± 0.2 ppm emerges for the TEPS of C-4a/10a in **1**. Hence, an upfield shift of 4.45 ppm results for the separate contribution of changing the steric orientation of the N-methyl group, so explaining the apparent anomalous behaviour of C-4a/10a (-1.48 ppm with respect to the parent amine instead of the expected downfield shift) upon protonation of **1** to yield $\mathbf{2}_{ax}$. The large difference between the TEPS estimated above and the APS ($+1.40$ ppm; see Table 2) measured for the carbons C-4a/10a in compound **1** leaves no doubt that the protonation shifts of these carbons depend on the steric orientation of the nitrogen lone-pair during protonation (or, rather, on the orientation of the N-alkyl group in the protonated form; see *Conclusions*).

A similar approach to the TEPS of C-4a/10a in **3** upon protonation to yield $\mathbf{4}_{ax}$ is not possible because, to the best of our knowledge, so far no data are available regarding the effect of an axial N-ethyl group on the ^{13}C NMR shifts of ring carbons to allow prediction of the chemical shifts of C-4a/10a in $\mathbf{3}_{ax}$. The strongly downfield shifting overall effect ($+4.99$ ppm; see Table 2) experienced by C-4a/10a in $\mathbf{4}_{ax}$, however, suggests that for **3** the difference between APS and TEPS of these carbons could be even more important than that found for **1**.

[a] If 7.4 ± 0.3 ppm (the effect of an equatorial *N*-methyl on the chemical shift of C-8a in *trans*-decahydroquinoline [8]) are added to 61.83 ppm (the chemical shift of C-4a/10a in *trans-cisoid-trans*-tetradecahydroacridine [11]), then a value of 69.23 ± 0.3 ppm is obtained for the chemical shift of C-4a/10a in $\mathbf{1} = \mathbf{1}_{eq}$, which is in excellent agreement with the experimental value (Table 2).

Another feature of stereochemical dependence emerges from the comparison between the protonation shifts of C-4a and those of C-10a on going from amines **5** and **7** to salts **6** and **8**, respectively (see Scheme 3). In both cases, the carbon involved in the *trans*-junction experiences a clearly weaker downfield shift (about one half) than its corresponding counterpart in the *cis* junction. One reason (but not the only one) for this striking difference in behaviour should be that the nitrogen atom is bonded equatorially to C-4a, whereas its bond to C-10a is axial.

A qualitatively similar difference in behaviour has been reported for the protonation shifts of the α-carbons in cyclohexylamines, where the contributions of an equatorial and of an axial NH_2 group have been estimated to $+0.60$ and $+2.28$ ppm, respectively [7].

However, comparison of the protonation shifts of C-4a in the *trans-cis* compounds **6** and **8** with those of C-4a in their *trans-trans* analogues $\mathbf{2}_{eq}$ and $\mathbf{4}_{eq}$ (Scheme 3) shows that beside the steric orientation of the own C–N bond (in all these compounds, the C-4a-N bond is equatorial!), the protonation shifts of α-carbons are also considerably influenced by changes in the geometry of more remote moieties of the molecule without being directly involved.

Comparison of the protonation shifts of either C-4a and C-10a within the pairs $\mathbf{2}_{eq}$–$\mathbf{4}_{eq}$ and **6**–**8**, respectively, shows that protonation shifts of α-carbons are sizeably influenced by the appearance of the additional carbon in the exocyclic N-alkyl group, too.

Steric effects on protonation shifts of carbons in β position

The effect of axial protonation of β-carbons (C-4, C-5, C-8a, and C-9a) of amines **1**, **3**, **5**, and **7** emerges straightforward from the chemical shift differences between compounds $\mathbf{2}_{eq}$–$\mathbf{1}_{eq}$, $\mathbf{4}_{eq}$–$\mathbf{3}_{eq}$, **6**–**5**, and **8**–**7**, respectively (Table 2 and Scheme 3). Axial protonation induces upfield shifts on all β-carbons; secondary ones (C-4, C-5) always exhibit considerably larger upfield shifts than do tertiary ones (C-8a, C-9a), in accordance with previous observations for sterically non-specific protonations [3, 5–7].

An evaluation of the TEPS for carbons C-4/5 and C-8a/9a on going from **1** to $\mathbf{2}_{ax}$ appears to be less accurate than it was for C-4a/10a (*vide supra*), since the prediction of the chemical shifts of these carbons in $\mathbf{1}_{ax}$ is suspect of too large error.

A tentative calculation of the chemical shifts of C-4/5 and C-8a/9a in $\mathbf{1}_{eq}$, using the chemical shifts of *trans-cisoid-trans*-tetradecahydroacridine [11] and the reported shift effects of an equatorial N-methyl group on appropriate carbons in *trans*-decahydroquinoline [8] affords 29.77 ± 0.2 and 41.55 ± 0.1 ppm (with an error of -1.26 ± 0.2 and $+0.56\pm0.1$ ppm, respectively, as compared to the measured values listed in Table 2). Thus, it is not justified to expect better accuracy in the prediction of the chemical shifts of the same carbons in $\mathbf{1}_{ax}$.

Comparison between the APS in the *trans-trans* compounds $\mathbf{2}_{eq}$, $\mathbf{4}_{eq}$ and those in their *trans-cis* analogues **6** and **8** (Scheme 3) reveals that protonation shifts of either secondary and tertiary β-carbons are even stronger influenced by the geometry of the carbon skeleton than α-carbons. Quite unexpectedly, by replacement of the C-8a/C-10a-*trans* junction with a *cis* junction, on going from either $\mathbf{2}_{eq}$ to **6** or $\mathbf{4}_{eq}$ to **8**, the protonation shifts of the remote carbons C-4 and C-9a

are clearly more influenced than those of the members of the sterically modified moiety (C-5 and C-8a).

On the other hand, comparison between either $\mathbf{2}_{eq}$–$\mathbf{4}_{eq}$ and **6**–**8** shows that, in contrast to α-carbons, the APS of secondary as well as tertiary β-carbons are little sensitive to the nature of the exocyclic N-alkyl group.

Steric effects upon protonation shifts of carbons in γ position

The APS of all γ-carbons are upfield oriented; their magnitudes lie between 1 and 3 ppm, depending on the geometry of the entire carbon skeleton (in Scheme 3, compare C-1 and C-3 within either $\mathbf{2}_{eq}$–**6** and $\mathbf{4}_{eq}$–**8**) and on the relative steric orientation of the nitrogen atom and the carbon of interest. Carbons oriented *gauche* always exhibit sizeably larger upfield shifts (-2 to -3 ppm) than carbons oriented *anti* (-1 to -1.4 ppm) to the nitrogen atom (in Scheme 3, compare C-9 with C-1/8 and C-3/6 in either of $\mathbf{2}_{eq}$ or $\mathbf{4}_{eq}$; compare also C-6, C-8, and C-9 with C-1 and C-3 in either of **6** or **8**). Like for β-carbons, the APS of γ-carbons show little sensitivity to the nature of the exocyclic N-alkyl group.

An evaluation of the TEPS of γ-carbons seems, as for β-carbons (*vide supra*), of poor reliability. Nevertheless, even a rough estimation for C-1 and C-9 in the protonation of $\mathbf{1}_{ax}$ to yield $\mathbf{2}_{ax}$[b] strongly supports that TEPS of γ-carbons depend in the same manner as shown above for APS on the relative steric orientation of the nitrogen atom and the carbon of interest (*i.e.* γ-*gauche* carbons are shifted more upfield than γ-*anti* carbons).

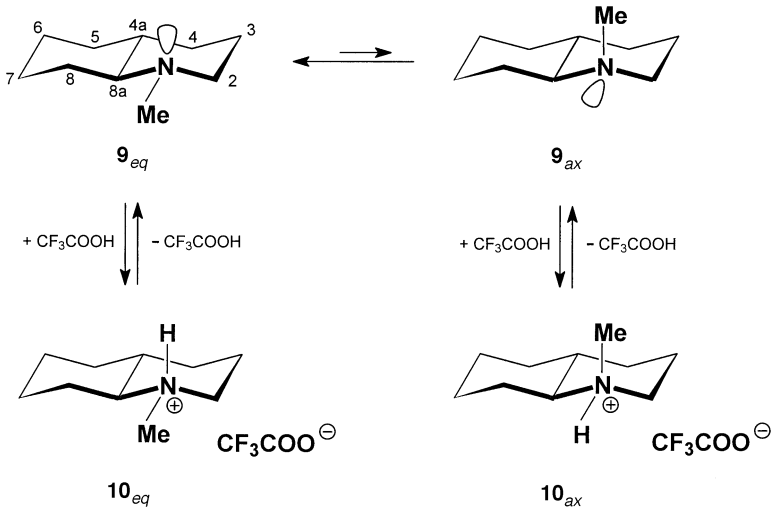
Steric effects upon protonation shifts of carbons in δ position

Upon axial protonation, in all compounds studied here δ-carbons (C-2 and C-7) undergo upfield shifts sizeably larger (from -1.7 to -2.1 ppm) than in any open-chain amine (from -0.2 to -1.2 ppm [3]) examined so far. The APS are somewhat influenced by the geometry of the entire carbon skeleton (compare either of C-2 or C-7 within the pairs $\mathbf{2}_{eq}$–**6** and $\mathbf{4}_{eq}$–**8** in Scheme 3); however, they neither depend on the path from the nitrogen atom to the carbon (compare C-2 with C-7 in either of **6** or **8**) nor on the nature of the exocyclic N-alkyl group (compare either of C-2 or C-7 within **6** and **8**).

The APS and TEPS of N-methyl-trans-decahydroquinoline

The fact that we could obtain no reliable evaluation of the TEPS for β-, γ- and δ-carbons in compound **1** prompted us to examine this feature for N-methyl-*trans*-decahydroquinoline (**9**), as the chemical shifts of most carbon atoms in the conformer $\mathbf{9}_{ax}$ (Scheme 4) can be rather accurately estimated using the increments for the effect of an axial N-methyl group upon the chemical shifts of ring carbons in *trans*-decahydroquinoline [8]. The ^{13}C chemical shifts thus calculated for $\mathbf{9}_{ax}$

[b] Assuming the shift effects of an axial N-methyl group upon appropriate carbons in *trans*-decahydroquinoline [8] to apply within ± 1 ppm in evaluating the chemical shifts of C-1 and C-9 in $\mathbf{1}_{ax}$, the TEPS should be -0.55 ± 1 ppm for C-1 and -2.26 ± 1 ppm for C-9.



Scheme 4

Table 3. Comparison of APS with TEPS and effective EPS of N-methyl-*trans*-decahydroquinoline (**9**)

^{13}C NMR chemical shifts and protonation shifts

			APS			TEPS	Effective EPS
	$\mathbf{9}^{a}_{eq}$	$\mathbf{10}^{a}_{eq}$	$(\delta_{\mathbf{10}_{eq}}-\delta_{\mathbf{9}_{eq}})$	$\mathbf{9}^{b}_{ax}$	$\mathbf{10}^{a}_{ax}$	$(\delta_{\mathbf{10}_{ax}}-\delta_{\mathbf{9}_{ax}})$	$(\delta_{\mathbf{10}_{ax}}-\delta_{\mathbf{9}_{eq}})$
C-2	57.94	57.09	−0.85	55.39±0.1	54.19	−1.20±0.1	−3.75
C-3	25.80	23.01	−2.79	19.79±0.1	18.03	−1.76±0.1	−7.77
C-4	32.59	30.11	−2.48	33.36±0.1	30.30	−3.06±0.1	−2.29
C-4a	41.84	39.54	−2.30	32.54±0.8	33.42	0.88±0.8	−8.42
C-5	33.06	32.49	−0.57	33.54±0.2	32.76	−0.78±0.2	−0.30
C-6	26.01	24.70	−1.31	c	25.0[d]	e	−1.01(?)
C-7	25.87	25.14	−0.73	c	25.0[d]	e	−0.87 (?)
C-8	30.47	27.37	−3.10	30.70±0.3	28.37	−2.33±0.3	−2.10
C-8a	69.25	69.95	0.70	65.09±0.2	65.84	0.75±0.2	−3.41
N–CH_3	42.59	40.54	−2.05	–	33.19	–	−9.40

[a] Chemical shifts in $CDCl_3$ downfield from internal *TMS* (Ref. [8]); [b] chemical shifts calculated using increments and chemical shift data from Ref. [8]; [c] increment not given; [d] chemical shift uncertain; [e] not estimated

and those measured [8] for the conformer $\mathbf{9}_{eq}$ and the N-diastereomeric triflates $\mathbf{10}_{eq}$ and $\mathbf{10}_{ax}$ allow to establish and to compare the APS and the TEPS of the most interesting carbon atoms in **9**. Inspection of Table 3 shows that APS differ sizeably from TEPS for most carbon atoms of **9**, the largest differences being observed for carbons in β positions.

For all β-carbons (C-3, C-4a, and C-8), with no exception always APS are more upfield than TEPS[c] and for the tertiary C-4a carbon even a change-over of the shift direction from APS to TEPS occurs.

For γ-carbons (C-4 and C-5), conversely, TEPS are somewhat more upfield than APS. The magnitudes of both APS and TEPS of γ-carbons, however, show the same manner of dependence on the relative steric orientation of the nitrogen atom and the carbon of interest: γ-carbons oriented *gauche* (C-4) are shifted about 2 ppm more upfield than carbons oriented *anti* (C-5 and C-8) to the nitrogen, thus confirming the behaviour already observed for the APS and suspected for the TEPS of γ-carbons in $\mathbf{2}_{eq}$, $\mathbf{4}_{eq}$, **6** and **8**.

Conclusions

The results of the present investigation definitely show that protonation shifts of saturated six-membered azaheterocyclic tertiary amines depend upon following stereochemical factors: (*i*) whether protonation occurs through an axial or an equatorial nitrogen lone-pair (the largest effects are observed for carbons in β positions); (*ii*) the steric relation between the nitrogen atom and the carbon of interest (for carbons in γ positions); (*iii*) the geometry of the entire carbon skeleton (for carbons in α, β, γ, δ, and likely also in more remote positions). All these features can be well rationalized qualitatively in terms of LEFS theory [4–6] according to which *N*-protonation induces changes in electron density on each carbon atom. Thus, in the protonated form each carbon becomes a new electric field source and so all carbon atoms influence each other. Hence, the ^{13}C protonation shifts do not only depend on the distances and stereochemical relations between the site of protonation (*i.e.* the nitrogen atom) and the observed carbons, but also on the distances and stereochemical relations between all carbon atoms. Therefore, the larger the amine molecule, the more difficult become quantitative predictions because more mutual interactions between carbon atoms have to be considered.

According to the LEFS theory, the observed differences between APS and TEPS of saturated azaheterocyclic tertiary amines should be determined in fact by the different steric orientation of the exocyclic N-alkyl group rather than by the steric orientation of the nitrogen lone-pair during protonation, and the group of *Morishima* [2] obviously has overestimated the role of stereospecificity of the σ inductive effect (*i.e.* the role of the geometry of the transmission path) with respect to differences between axial and equatorial protonation shifts.

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[c] The group of *Morishima* [2] reached just a reverse conclusion on comparing the protonation shifts of β-carbons in quinuclidine and N–H piperidines (which they allegedly considered as model compounds for equatorial protonation through a zigzag transmission path) with those of β-carbons in quinolizidine and N-methylpiperidines (as model compounds for axial protonation through a folded transmission path). The data of the present paper and of others [5–7], however, show that comparisons between protonation shifts in different compounds can not be conclusive, as any change in the structural formula, even not affecting the transmission path, can induce considerable changes of protonation shifts (*e.g.*, compare the APS of the β-carbons C-4 and C-9a in $\mathbf{2}_{eq}$ with those of the corresponding carbons in **6** in Scheme 3: despite of absolutely identical transmission paths from the nitrogen atom to these carbons in $\mathbf{2}_{eq}$ and **6**, the APS differ by 1 ppm and 1.1 ppm, respectively).

Experimental

The NMR instruments, the parameters of spectra acquirement, and the synthetic routes used in this work have been described in the previous paper (part 19) of this series [1].

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