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Hydroacridines XIX [1]. ^{13}C NMR Spectra of Several *N*-Alkyl-tetradecahydroacridines and their Protonated Species: Investigation of the *N*-Epimeric Equilibria of the *N*-Alkyl Groups in the Amines and in the Salts

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Summary. (4aα,8aβ,9aβ,10aα)-Tetradecahydro-10-methylacridin, (4aα,8aβ,9aβ,10aα)-10-ethyl-tetradecahydroacridin, (4aα,8aα,9aβ,10aα)-tetradecahydro-10-methylacridine, (4aα,8aα,9aβ,10aα)-10-ethyl-tetradecahydroacridin and their products of protonation with trifluoroacetic acid were studied by ^{13}C NMR spectroscopy. The first two amines give rise to a pair of *N*-diastereomeric salts, whereas the latter two yield only the salts with equatorial *N*-alkyl groups. The *N*-epimeric equilibria of the *N*-alkyl groups (equatorial-axial) in the salts and in the amines are discussed.

Keywords. Acridines, tetradecahydro; N-Epimeric equilibria; ^{13}C NMR.

Hydroacridine, 19. Mitt. [1]**. ^{13}C-NMR-Spektren einiger *N*-Alkyl-tetradecahydroacridine und deren protonierter Species: Untersuchung der *N*-epimeren Gleichgewichte der *N*-Alkylgruppen in den Aminen und in den Salzen**

Zusammenfassung. (4aα,8aβ,9aβ,10aα)-Tetradecahydro-10-methylacridin, (4aα,8aβ,9aβ,10aα)-10-Ethyl-tetradecahydroacridin, (4aα,8aα,9aβ,10aα)-Tetradecahydro-10-methylacridin, (4aα,8aα,9aβ,10aα)-10-Ethyl-tetradecahydroacridin und deren Protonierungsprodukte mit Trifluoressigsäure wurden ^{13}C-NMR-spektroskopisch untersucht. Die beiden erstgenannten Amine ergeben jeweils ein Paar *N*-diastereomerer Salze, während aus den beiden letzteren nur die Salze mit äquatorialen *N*-Alkylgruppen entstehen. Die *N*-epimeren Gleichgewichte der *N*-Alkylgruppen (äquatorial-axial) in den Salzen und in den Aminen werden diskutiert.

Introduction

The equilibria of *N*-epimeric pairs of various *N*,*C*-polymethylpiperidinium [2–5] and *N*-methyl-*trans*-decahydroquinolinium salts [6] have been the object of considerable attention. Since a comparison with tetradecahydroacridinium salts

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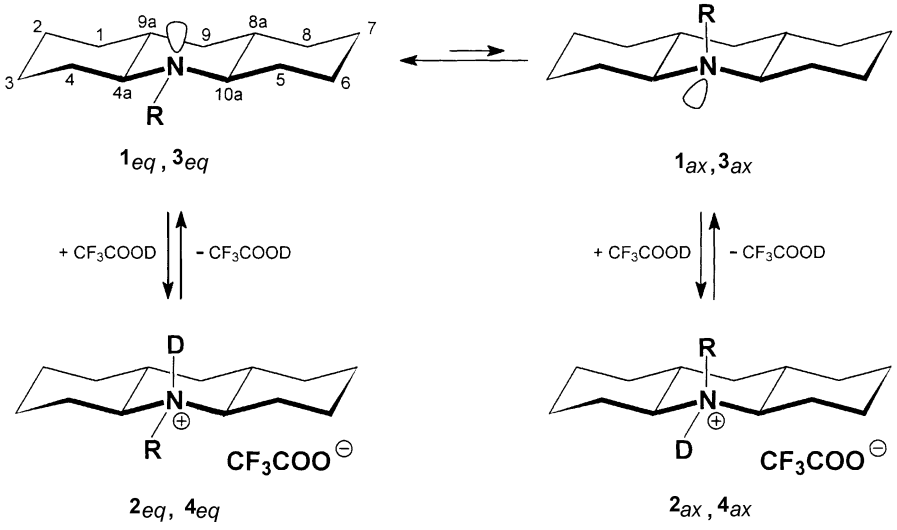
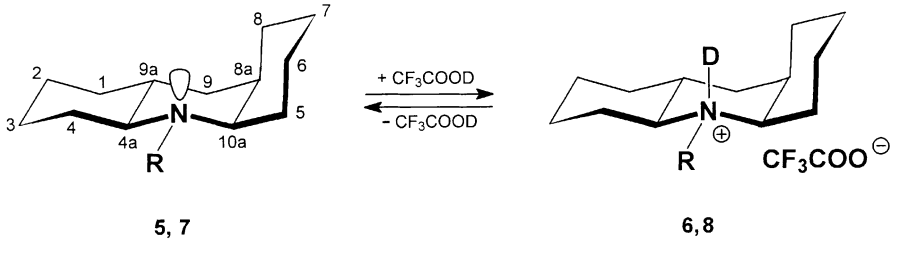
should be of interest, we have examined the salts formed by 'protonation' of (4aα,8aβ,9aβ,10aα)-tetradecahydro-10-methylacridine (**1**), (4aα,8aβ,9aβ,10aα)-10-ethyl-tetradecahydroacridine (**3**), (4aα,8aα,9aβ,10aα)-tetradecahydro-10-methylacridine (**5**), and (4aα,8aα,9aβ,10aα)-10-ethyl-tetradecahydroacridine (**7**) with deuterated trifluoroacetic acid from this point of view.

As trifluoroacetic acid-*d* was used for salt formation, actually '*deuteronation*' should be the correct term to be used. For convenience, however, we will use the term '*protonation*' within this paper. The isotope effect exerted by substitution of hydrogen by deuterium on the ^{13}C NMR chemical shifts of the carbon atoms in positions α and β with respect to the nitrogen in the salts (*i.e.*, in β and γ positions, respectively, to the deuterium) results mostly in an upfield shift of less than 0.2 ppm [7]. The isotope effect on more remote carbons is expected to be within or below the limits of experimental error.



1*eq*, **1***ax*, **2***eq*, **2***ax*: *R* = Me; **3***eq*, **3***ax*, **4***eq*, **4***ax*: *R* = Et

Scheme 1



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

Scheme 2

Upon protonation, amines **1** and **3** each give rise to a pair of *N*-diastereomeric triflates ($\mathbf{2}_{eq}$, $\mathbf{2}_{ax}$ and $\mathbf{4}_{eq}$, $\mathbf{4}_{ax}$, respectively, Scheme 1), whereas amines **5** and **7** yield only the salts with equatorial N^+-alkyl groups (**6** and **8**; Scheme 2). The quantitative parameters of the equilibria of the N^+-alkyl groups within the pairs $\mathbf{2}_{eq}$, $\mathbf{2}_{ax}$ and $\mathbf{4}_{eq}$, $\mathbf{4}_{ax}$ were determined through quantitative ^{13}C and ^{1}H NMR, respectively. In addition, we suggest a possible new way to estimate the free energy differences (ΔG°) of the *N*-alkyl groups in free amines, considering those of their salts and the solvation power of the solvent used.

Results and Discussion

^{13}C NMR signal and stereostructural assignments

The steric orientations of the N^+-alkyl groups in the triflates $\mathbf{2}_{eq}$, $\mathbf{2}_{ax}$, $\mathbf{4}_{eq}$, $\mathbf{4}_{ax}$, **6** and **8** were established by comparison of their ^{13}C NMR spectra with those of the parent amines **1**, **3**, **5**, and **7**, respectively. Except for $\mathbf{4}_{ax}$, for all compounds full signal assignments of the ring carbons could be secured by the 2D INADEQUATE technique. For the exocyclic N^+-CH_3 and N^+-CH_2CH_3 groups in the salts $\mathbf{2}_{eq}$, $\mathbf{2}_{ax}$, $\mathbf{4}_{eq}$, $\mathbf{4}_{ax}$, **6** and **8**, the stereochemical assignments were performed based on the presence or absence of the clearly observable mutual γ-*gauche* effects with the bridgehead carbons C-8a and C-9a (for details, see discussion of specific compounds). For amine **1** and earlier signal assignment already exists [8] containing am ambiguity which is now eliminated. The ^{13}C NMR chemical shifts and signal assignments of compounds **1**–**8** are presented in Table 1.

The trifluoroacetate of amine **1** exhibits two sets of sharp resonances: eight signals of higher intensity and another eight of lower intensity, obviously a two-species spectrum arising from the equilibrating pair of *N*-epimeric salts $\mathbf{2}_{eq}/\mathbf{2}_{ax}$. Owing to the small number of signals of $\mathbf{2}_{eq}$ and $\mathbf{2}_{ax}$ and to a sufficient portion of the minor epimer (see next section), for both $\mathbf{2}_{eq}$ and $\mathbf{2}_{ax}$ the complete signal assignments could be achieved by a 2D INADEQUATE experiment on the mixture. In the spectrum with higher intensity (*i.e.* that of the major epimer), the signal positions show only the shifts induced by *N*-protonation [9] and indicate no change in geometry with respect to the parent amine **1**[a]. On the other hand, in the spectrum of the minor epimer very large upfield shifts are observed for the bridgehead-carbons C-8a/9a (−8.43 ppm) and the N^+-CH_3 carbon (−8.97 ppm) that may not be due solely to protonation and can be rationalized only by the γ-*gauche* interactions of these carbons with the axial N^+-methyl group in $\mathbf{2}_{ax}$. Therefore, the major epimer has to be assigned structure $\mathbf{2}_{eq}$ with an equatorially oriented N^+-methyl group.

The trifluoroacetate of amine **3** also gives a two-species spectrum arising from the equilibrating *N*-epimeric salts $\mathbf{4}_{eq}$ and $\mathbf{4}_{ax}$. By the same reason as shown for the

[a] According to investigations on *C*, *N*-dimethyldecahydroquinolines (Ref. [8]) sterically related to our amines, for **1** the amount of conformer $\mathbf{1}_{eq}$ should be at least 95% and for **5** that 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 practically identical with that of $\mathbf{1}_{eq}$. The spectra of **3**, **5**, and **7** correspond to those of their equatorial *N*-alkyl epimers.

Table 1. ^{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** (± 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 downfiled 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]

pair $\mathbf{2}_{eq}/\mathbf{2}_{ax}$ (*vide supra*), structure $\mathbf{4}_{eq}$ was ascribed to the major epimer and structure $\mathbf{4}_{ax}$ to the minor one. In this case, however, because of too low content of $\mathbf{4}_{ax}$ in the equilibrium mixture, signal assignments were possible only for $\mathbf{4}_{eq}$ through the 2D INADEQUATE spectrum. Nevertheless, an almost complete signal

assignment for $\mathbf{4}_{ax}$ could be achieved *via* chemical shift comparisons with the triflates $\mathbf{2}_{eq}$, $\mathbf{2}_{ax}$, and $\mathbf{4}_{eq}$, relative signal intensities, and a DEPT-135 experiment run on the equilibrium mixture; only the signals of C-2/7 and C-3/6, too close to each other to be resolved, remained ambiguous.

The triflates of both **5** and **7** exhibit only one set of signals, whose chemical shifts point to structures with equatorial N^+-alkyl groups (**6** and **8**).

The equilibria of the N-epimeric pairs of triflates $\mathbf{2}_{eq}$–$\mathbf{2}_{ax}$ *and* $\mathbf{4}_{eq}$–$\mathbf{4}_{ax}$

The main quantitative parameters of the *N*-epimeric equilibria of the triflates $\mathbf{2}_{eq}$–$\mathbf{2}_{ax}$ and $\mathbf{4}_{eq}$–$\mathbf{4}_{ax}$, respectively, are presented in Table 2. The ratio $\mathbf{2}_{eq}$:$\mathbf{2}_{ax}$ was determined by quantitative ^{13}C NMR spectroscopy by averaging the integration data for five well separated pairs of signals of correspondent carbons (C-2/7, C-3/6, C-9, C-4a/10a, and N^+-CH_3); the five individual values emerging from these pairs of signals were consistent within ±2%. The ratio $\mathbf{4}_{eq}$:$\mathbf{4}_{ax}$ was determined by integration of the H-4a/10a and N^+-CH_2 proton signals well separated in the ^{1}H NMR spectrum of the mixture (see Experimental); the accuracy was also ±2%.

The largely increased equilibrium proportion of the epimers with axial *N*-alkyl groups in salts ($\mathbf{2}_{ax}$ and $\mathbf{4}_{ax}$, respectively) as compared to the free parent amines (expected: $\mathbf{1}_{ax}$: ≤5%, $\mathbf{3}_{ax}$: ≤2%; see discussion below and footnote[a]) is a general feature whose main explanation is the easier solvation of the equatorial N^+-H bonds owing to which the salts with axial N^+-alkyl groups are more stabilized by solvation than are their epimers with equatorial N^+-alkyl groups [3, 5]. Hence, the higher the solvation ability of the solvent, the more reduced the free-energy difference between the equilibrating *N*-epimers. For *N*-diastereomeric 1-*cis*-2,6-trimethylpiperidinium salts, where the steric relations of the *N*-methyl group are rather similar to those in $\mathbf{2}_{eq}$/$\mathbf{2}_{ax}$, $-\Delta G^\circ$ values ranging from 0.46 to 2.09 kJ · mol^{-1} have been reported (see Table 3) in dependence on the solvation power of the solvents (and on experimental errors, perhaps). The value of 1.31 kJ · mol^{-1} found by us for the free energy difference between $\mathbf{2}_{eq}$ and $\mathbf{2}_{ax}$ compares very well to the mean of the extreme values given above.

It seems reasonable to expect the $-\Delta G^\circ$ value for the free amine *N*-epimers $\mathbf{1}_{eq}$–$\mathbf{1}_{ax}$ also to be comparable to that of free 1-*cis*-2,6-trimethylpiperidine, for which 7.7±0.1 kJ · mol^{-1} (cyclohexane, 288 K) has been reported [10][b]. If this is

Table 2. Equilibrium constants (K) and free energy differences (ΔG°) of the *N*-epimeric pairs of deuterotrifluoroacetates $\mathbf{2}_{eq}$–$\mathbf{2}_{ax}$ and $\mathbf{4}_{eq}$–$\mathbf{4}_{ax}$ in $CDCl_3$

N-Epimers (equilibrium ratio ±2%)	K_{296}	$-\Delta G^\circ_{296}$ (kJ · mol^{-1})
$\mathbf{2}_{eq}$ (63%): $\mathbf{2}_{ax}$ (37%)	1.71±0.15	1.31±0.21
$\mathbf{4}_{eq}$ (86%): $\mathbf{4}_{ax}$ (14%)	6.29±1.04	4.49±0.41

[b] This is the only firm value we could find in the literature for this compound (in Ref. [5], $-\Delta G^\circ$> 5.44 kJ · mol^{-1} with no upper limit is given); for the *N*-methyl-*trans*-decahydroquinoline conformers, a $-\Delta G^\circ$ value of 7.53 to 10.25 kJ · mol^{-1} in $CDCl_3$ has been estimated (Ref. [6]).

Table 3. ΔG° values of 1-*cis*-2,6-trimethylpiperidinium salts as determined in various solvents[a]

Salt/Solvent	$-\Delta G^\circ$ ($kJ \cdot mol^{-1}$)	*T (K)*	Method of determination	Ref.
Perdeuteroacetate/CD_3COOD	0.46	306	^{1}H NMR	[3]
Perdeuteroacetate/CD_3COOD	0.71	311	^{1}H NMR	[2]
Formate/HCOOH	1.46	306	^{1}H NMR	[3]
Hydrochloride/H_2O	1.50	296	^{1}H NMR	[4]
Hydrochloride/D_2O	1.84	308	^{13}C NMR	[5]
Hydrochloride/H_2O	2.09	306	^{1}H NMR	[3]
Trifluoroacetate/CF_3COOH	1.92	311	^{1}H NMR	[2]

[a] Values reported earlier in $kcal \cdot mol^{-1}$ were converted to $kJ \cdot mol^{-1}$ using $1\,cal = 4.184\,J$

true, the effect of preferential solvation of $\mathbf{2}_{ax}$ by $CDCl_3$ in reducing the free energy difference of $\mathbf{2}_{eq}/\mathbf{2}_{ax}$ relative to $\mathbf{1}_{eq}/\mathbf{1}_{ax}$ can be estimated to approximately $7.70\,kJ \cdot mol^{-1}$–$1.31\,kJ \cdot mol^{-1} \cong 6.4\,kJ \cdot mol^{-1}$, and an equilibrium ratio of *ca.* 96% $\mathbf{1}_{eq}$: 4% $\mathbf{1}_{ax}$ emerges which is in agreement with other indirect deduction methods (see footnote[a]). Beside preferential solvation, longer C–N bonds in the salts than in free amines also have been considered as a possible cause of free energy difference attenuation [5]; the striking solvent dependence of $-\Delta G^\circ$ shown in Table 3, however, leaves no doubt that solvation provides by far the main contribution.

The direct determination of ΔG° values for nitrogen inversion epimers of free saturated azaheterocyclic amines is associated with important technical difficulties and a low degree of accuracy because (*i*) due to the very high rate of nitrogen inversion at ambient temperature, direct measurement of *N*-epimer ratios generally is only possible at temperatures below $-80°C$ in solvents with freezing points lower than $-100°C$, and (*ii*) ΔG° values of free amines are much larger than those of their salts, and large ΔG° values (for minor epimer contents less than *ca.* 5%) are notoriously hard to measure accurately. Therefore, several more convenient (but not more accurate!) procedures of indirect determination have been developed during the course of time (for a short survey, see Ref. [6]).

A new and very convenient indirect procedure could, perhaps, arise from the solvation effect discussed above. It appears fairly likely that a given solvent will produce, through the effect of preferential equatorial solvation, approximately equal attenuation of the ΔG° values for the salts epimers of any amine; thus, if the ΔG° value for the salt epimers in a given solvent and the magnitude of the attenuating effect of that solvent are known, the ΔG° value for the corresponding free amine epimers should be very easy to estimate. For example, on assuming that the ΔG° attenuating effect of $CDCl_3$ as estimated above to *ca.* $6.4\,kJ \cdot mol^{-1}$ applies also to amine $\mathbf{3}_{eq}$–$\mathbf{3}_{ax}$, and its salts $4_{eq} - 4_{ax}$, a tentative estimation of the free energy difference for the amine epimers $\mathbf{3}_{eq}$–$\mathbf{3}_{ax}$ leads to: $-\Delta G^\circ_{\text{N-Et (3)}} = (4.49 \pm 0.41)\,kJ \cdot mol^{-1} + 6.4\,kJ \cdot mol^{-1} = ca.\ 10.9 \pm 0.4\,kJ \cdot mol^{-1}$ (*i.e.*, 98.8% $\mathbf{3}_{eq}$: 1.2% $\mathbf{3}_{ax}$). Although this value could appear a little high if compared with *N*-ethyl-*trans*-decahydroquinoline for which $-\Delta G^\circ_{\text{N-Et}} = 8.78\,kJ \cdot mol^{-1}$ has been estimated [6] (for various cyclohexane derivatives, $-\Delta G^\circ_{\text{C-Et}}$ values ranging from 7.28 to $9.49\,kJ \cdot mol^{-1}$ have been reported [11–13]), this result is nevertheless

encouraging as $6.4\,kJ \cdot mol^{-1}$ probably is not yet the best value for the ΔG° attenuating effect of $CDCl_3$ and could be susceptible of some refinement. On the other hand, a somewhat higher ΔG° value for the *N*-ethyl group in **3** than in *N*-ethyl-*trans*-decahydroquinoline could be justified by the higher rigidity of the piperidine ring in **3** than in N-ethyl-*trans*-decahydroquinoline.

The total absence of *N*-epimers with axial N^+-alkyl groups among the triflates of amines **5** and **7** is well justified by the double *syn*-diaxial steric interaction (at least $15.5\,kJ \cdot mol^{-1}$ each [14]) that an axial N^+-alkyl group would have to undergo with both of the C-6 and C-8 methylene groups and which obviously cannot be counterbalanced by the ΔG° attenuating solvation effect of $CDCl_3$.

Experimental

General

All NMR measurements were run at 296 K on a JEOL GX 400 NMR spectrometer (^1H: 399.65 MHz, ^{13}C: 100.4 MHz) equipped with a LSI 11/73 computer and a JEOL JEC 32 dataprocessor using solutions ranging from 1.5–2.5 *M* in $CDCl_3$ with internal *TMS* in 5 mm sample tubes. The 2D INADEQUATE experiments were performed using a composite pulse sequence [15] and quadrature detection in f_1 and f_2 with the following instrumental settings: 1792 scans (64 h measurement time), $\tau = 3/4\ J = 21.4$ ms (for $J = 35$ Hz), 32 data points in f_1 with zero filling to 64, 16384 data points in f_2 (digital resolution 0.8 Hz)

Syntheses

The syntheses of amines **1**, **3**, **5**, and **7** have already been described elsewhere [16]. The solutions of the salts $\mathbf{2}_{eq,ax}$, $\mathbf{4}_{eq,ax}$, **6**, and **8** were prepared from solutions of the parent amines, in $CDCl_3$ by adding slowly, under shaking by hand, small drops (pipette) of CF_3COOD until turbidity was produced by the first excess drop of acid (the salts are soluble in $CDCl_3$, whereas CF_3COOD is not miscible with it). Upon standing, the probe solution became soon clear as the excess acid raised to the solution surface.

Characteristic ^1H NMR signals of the N-diastereomeric salts (δ_H, 400 MHz, $CDCl_3$)

$\mathbf{2}_{eq}$: 2.68 (td, $J = 10.6$, 10.6, 3.3, 3.3, and 3.3 Hz, H-4a/10a), 2.83 (s, N^+-CH_3) ppm; $\mathbf{2}_{ax}$: 3.07 (td, $J = 11.8$, 11.8, 3.3, 3.3, and 3.3 Hz, H-4a/10a) ppm, 2.70 (s, N^+-CH_3) ppm; $\mathbf{4}_{eq}$: 2.77 (td, $J = 11$, 11, 3.5, 3.5, and 3.5 Hz, H-4a/10a) ppm, 3.35 (q, $J = 7$, 7, and 7 Hz, N^+-CH_2-) ppm; $\mathbf{4}_{ax}$: 3.08 (td, $J = 11$, 11, 3.5, 3.5, and 3.5 Hz, H-4a/10a) ppm, 3.14(q, $J = 7$, 7, and 7 Hz, N^+–CH_2–) ppm.

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