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Determination of the conformations and relative configurations of exocyclic amines

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The conformations and relative configurations of 20 amines, classified according to the following labeling scheme, were analyzed. Series a comprised compounds derived from *N*-(1-phenylethyl)cyclohexanamine, b comprised derivatives of *N*-[1-(naphthalen-2-yl)ethyl]cyclohexanamine, c comprised derivatives of *N*-(diphenylmethyl)cyclohexanamine, and d comprised derivatives of *N*-(propan-2-yl)cyclohexanamine. The compounds were labeled as follows: 1 indicates cyclohexanamine, 2 indicates 2-methylcyclohexanamines, 3 indicates 3-methylcyclohexanamines, 4 indicates 4-methylcyclohexanamines, and 5 indicates 4-*tert*-butylcyclohexanamines. These compounds were prepared without the use of stereoselective induction and, therefore, all expected stereoisomers were observed. Structural assignments were established by ^{1}H, ^{13}C, and ^{15}N NMR.

Keywords: ^{1}H; ^{13}C; and ^{15}N NMR; conformation; configuration; exocyclic amine

Introduction

Knowledge of the absolute configuration and conformation of exocyclic amines is of great importance, particularly for compounds with biological activity. Also, determination of the stereoselectivity of a reaction is important for both the pharmaceutical and agricultural industries. The exocyclic amines are a key group of compounds because they are the source of many interesting substances in these industries.

Some of the amines reported here have been used as chiral inductors, particularly the derivatives of 1-phenylethylamine[1] and 1-(naphthalen-2-yl)ethylamine.[2] The cyclohexanamines and their *N*-substituted derivatives form a group of secondary amines with a variety of basicities that can be used in the synthesis of complex molecules; currently, *N*-(propan-2-yl)cyclohexanamine[3] is used as a base for the deprotonation of slightly acidic compounds through the preparation of a lithium amide.

This paper reports the structural analysis of 20 amines: the symmetric secondary cyclohexanamines **1c, 1d, 4c, 4d, 5c**, and **5d**; compounds **1a, 1b, 4a, 4b, 5a**, and **5b**, which contain one asymmetric atom; compounds **2c, 2d, 3c**, and **3d**, which have two stereogenic atoms; and compounds **2a, 2b, 3a**, and **3b** which have three stereogenic atoms (Fig. 1).

These compounds were assigned as diastereomeric mixtures and presented all the expected stereoisomers. Analysis of the mixtures allowed determination of the additive effects of the NMR chemical shifts.

Some of these compounds have been prepared by stereoselective reduction of imines[4]; the 1-phenylethanamine has been used as an asymmetric inductor. They have been used as models for absolute configuration, recognized by means of chiroptical techniques because of their capacity to form host/guest complexes.[5] For this reason, determination of their geometry was interesting, and NMR was used because it is the most robust and facile method for elucidating a conformation in the solution state.

The relative position of each substituent on the cyclohexane was determined using ^{1}H, ^{13}C, and ^{15}N NMR. The ^{1}H chemical shift indicated the environment of each hydrogen, and the coupling patterns provided evidence for the conformation. The ^{13}C NMR spectra displayed known $\gamma_{anti}/\gamma_{gauche}$ effects that allowed for the elucidation of the absolute orientation of the electronegative groups. The ^{15}N NMR was a valuable method of analysis for determining conformation because the difference between the chemical shifts of the equatorial and axial positions was at least 7 ppm.[6]

Results and Discussion

The compounds studied in the present work were prepared by reduction of the corresponding cyclohexylidene-*N*-(1-arylethyl)amine, cyclohexylidene-*N*-(isopropyl)amine, or cyclohexylidene-*N*-(diphenylmethyl)amine derivatives by $NaBH_4$. Since the reduction reaction was not stereoselective, all possible isomers were obtained in the reaction mixture. The NMR spectral assignments were made based on one- and two-dimensional (1D and 2D, respectively) techniques. Connectivity was established using heteronuclear and homonuclear correlation spectroscopies (COSY, NOESY, and HETCOR ^{13}C–^{1}H), and the type of carbon was determined by APT (attached proton test) or DEPT (distortionless enhancement by polarization transfer) spectra.

The secondary cyclohexanamines preferred a chair conformation, and the amine groups in the compounds without substituents (**1a**–**1d**) were present in the equatorial position. The ^{1}H NMR spectra (Table 1) provided robust information about the conformation of the six-member rings as well as the relative positions of the amine groups. In the case of the cyclohexane anchored by the

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Table 1. ^{1}H NMR of the amine series **a** (**1a, 2a, 3a, 4a**, and **5a**)

Compounds	Isomers	1	2	3	4	5	6	7	R
1a	–	2.29	1.72	1.66	1.55	1.66	1.99	3.96	–
			1.13	1.13		1.13	1.13		
2a	*lu*	2.06	1.20	1.06	1.24	1.41	1.01	3.90	0.98
				1.69	1.62	1.68	1.83		
	ll	1.85	1.30	1.06	1.38	1.32	1.22	3.90	0.97
				1.69	1.57	1.41	1.83		
	ul	2.52	2.05	1.35	1.35	1.28	1.14	3.91	1.09
				1.60	1.54	1.63	1.20		
	uu	2.50	1.71	1.43	1.41	1.38	1.51	4.00	0.93
					1.66	1.58	1.65		
3a	*RRR*	2.69	1.39	1.73	1.54	1.38	1.18	3.98	0.82
			1.39		1.58	1.48	1.72		
	SRS	2.69	1.18	1.73	1.42	1.40	1.30	3.98	0.85
			1.42		1.58	1.48	1.63		
	RRS	2.27	0.79	1.26	0.82	1.34	0.95	3.87	0.88
			1.75		1.02	1.72	2.00		
	SRR	2.29	0.98	1.30	0.82	1.34	0.72	3.87	0.86
			1.55		1.02	1.70	2.00		
4a	*cis*	2.51	1.4	1.27	1.29	1.27	1.46	3.89	0.81
			1.47	1.43		1.43	1.56		
	trans	2.21	1.11	0.85	1.29	0.81	1.01	3.95	0.92
			1.70	1.62		1.62	2.01		
5a	*cis*	2.68	1.34	1.27	0.99	1.27	1.27	3.98	0.79
			1.7	1.51		1.51	1.85		
	trans	2.23	1.17	0.95	0.94	0.85	0.95	3.84	0.84
			1.89	1.67		1.70	2.09		
1b	–	2.40	1.12	1.12	1.55	1.06	1.1	4.85	–
			1.84	1.66	1.55	1.63	1.99		
2b	*lu*	2.20	1.32	0.93	1.29	1.22	0.93	4.79	1.04
				1.74	1.69	1.72	2.01		
	ll	1.94	1.32	0.93	1.29	0.93	0.93	4.79	1.07
				1.74	1.60	1.72	2.01		
	ul	2.65	2.01	1.32	1.34	1.20	1.46	4.79	1.13
				1.45	1.43	1.63	1.46		
	uu	2.57	1.82	1.45	1.34	1.30	1.46	4.79	1.00
				1.45	1.66	1.55	1.62		
3b	*RRR*	2.89	1.62	1.86	1.07	1.54	1.10	4.82	0.91
			1.62		1.64	1.64	1.70		
	SRS	2.88	1.31	1.86	1.07	1.54	1.49	4.83	0.93
			1.69		1.64	1.64	1.64		
	RRS	2.49	0.91	1.31	0.83	1.17	0.99	4.95	0.95
			1.95		1.55	1.72	2.10		
	SRR	2.50	1.03	1.26	0.83	1.22	0.82	4.95	0.93
			1.95		1.55	1.71	2.10		
4b	*cis*	2.67	1.50	1.33	1.36	1.33	1.55	4.80	0.95
			1.63	1.50		1.50	1.55		
	trans	2.37	1.18	0.86	1.34	0.78	1.09	4.86	0.82
			1.87	1.65		1.64	2.03		
5b	*cis*	2.81	1.48	1.29	0.97	1.37	1.29	4.72	0.87
			1.80	1.55		1.57	1.90		
	trans	2.33	1.09	0.87	0.87	0.87	0.91	4.86	0.78
			1.93	1.72		1.72	2.09		
1c	–	2.50	1.20	1.24	1.23	1.25	1.20	5.13	–
			2.04	1.78	1.61	1.78	2.04		
2c	*cis*	2.66	1.97	1.45	1.42	1.50	1.50	5.04	1.05
				1.45	1.61	1.68	1.65		

Table 1. (*Continued*)

Compounds	Isomers	1	2	3	4	5	6	7	R
	trans	2.07	1.22	1.09	1.69	1.78	1.03	5.13	1.15
				1.73	1.69	1.78	2.27		
3c	*cis*	2.51	0.84	1.41	1.10	1.29	0.93	5.05	1.00
			2.12		1.69	1.79	1.68		
	trans	2.93	1.29	1.87	1.59	1.59	1.08	5.18	0.97
			1.79		1.69	1.69	2.12		
4c	*cis*	2.78	1.20	1.58	1.41	1.58	1.20	5.07	1.02
			2.12	1.76		1.76	2.12		
	trans	2.46	0.97	1.40	1.61	1.40	0.97	5.16	0.95
			1.76	1.58		1.58	1.76		
5c	*cis*	2.84	1.37	1.57	1.02	1.57	1.37	4.97	0.91
			1.93	1.61		1.61	1.93		
	trans	2.38	1.12	0.90	1.02	0.90	1.12	5.10	0.86
			2.13	1.74		1.74	2.13		
1d	–	2.47	1.55	1.00	1.19	1.00	1.55	2.94	–
			1.83	1.65	1.65	1.65	1.83		
2d	*cis*	2.53	1.76	1.27	1.13	1.19	1.21	2.75	0.74
				1.37	1.24	1.48	1.32		
	trans	1.90	1.08	1.58	1.10	1.13	0.88	2.75	0.82
				1.58	1.48	1.58	1.79		
3d	*cis*	2.40	0.56	1.29	1.00	1.17	0.74	2.87	0.79
			1.77		1.49	1.61	1.51		
	trans	2.78	1.17	1.61	–	1.37	0.93	2.78	0.79
			1.42			1.37	1.77		
4d	*cis*	2.55	0.90	1.35	1.42	1.35	0.90	2.73	0.74
			1.72	1.35		1.35	1.72		
	trans	2.29	0.80	1.11	1.15	1.11	0.80	2.80	0.71
			1.52	1.30		1.30	1.52		
5d	*cis*	2.83	1.30	1.05	0.81	1.05	1.30	2.78	0.77
			1.76	1.45		1.45	1.76		
	trans	2.39	0.92	0.96	0.85	0.96	0.92	2.92	0.77
			1.90	1.70		1.70	1.90		

^3J ($^1H_{ax}$, $^1H_{eq}$) = 3.7 ± 0.4 Hz; ^3J ($^1H_{eq}$, $^1H_{eq}$) = 4.2 ± 1 Hz; ^3J ($^1H_{ax}$, $^1H_{ax}$) = 10.4 ± 1 Hz.

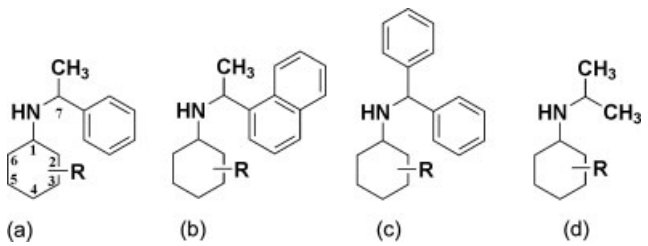

Figure 1. Structures of the amine derivatives analyzed. For **1**, R = H; **2**, R = CH_3 at C2; **3**, R = CH_3 at C3; **4**, R = CH_3 at C4; **5**, R = *tert*-butyl at C4.

tert-butyl group, the amine group was present in the equatorial or the axial position. If the ^1H was present in the equatorial position, its multiplicity was a quintet and the magnitudes of the axial–equatorial and equatorial–equatorial coupling constants were the same ($^3J_{H,H}$ = 3.6 Hz). For the case of the ^1H in the axial position, the resonance appeared as a triplet of triplets, with two axial–axial coupling constants of 10 Hz and two axial–equatorial coupling constants of 3.6 Hz. The equatorial hydrogen atoms were high-frequency shifted by 0.59 ± 0.18 ppm with respect to the axial hydrogen atoms.

The strategy for assigning the configuration of compounds **3a** and **3b** was to prepare the ketimines using the optically pure (*R*) or (*S*) 3-methylcyclohexanone and (*R*) or (*S*) 1-phenylethanamine, which were used to identify the epimers present in these compounds since the absolute configuration at C-3 and C-7 were known. This method provided only the *cis* and *trans* isomers. For instance, the *trans* isomer of compound **3a**, with a configuration *RRR*, in which the amine group was in the axial position, displayed the ^1H as a pseudo-quintet signal (δ_H = 2.69, $^3J_{H,H}$ = 4.5); the *cis* isomer (*SRR*), with the amine group in the equatorial position, split the same hydrogen as a triplet of triplets (δ_H = 2.29, $^3J_{H,H}$ = 10.9 and 4.0). The same observations were made for the epimers *SRS* and *RRS* as well as for compound **3b**.

Compounds **3c** and **3d** contained two stereogenic atoms (C1 and C3); therefore, each compound mixture included a pair of diastereomers, which was evident in the NMR spectra. These compounds were identified by the relative position of the *cis*/*trans* isomers (*l* and *u*, respectively). The *cis* isomers of compound **3c** contained the amine group in the equatorial position, and the resonance of the hydrogen bond to C1 was displayed as a triplet of triplets with two coupling constants (δ_H = 2.51, $^3J_{H,H}$ = 10.8 and 3.9). The *trans* isomers preferred to position the amine group

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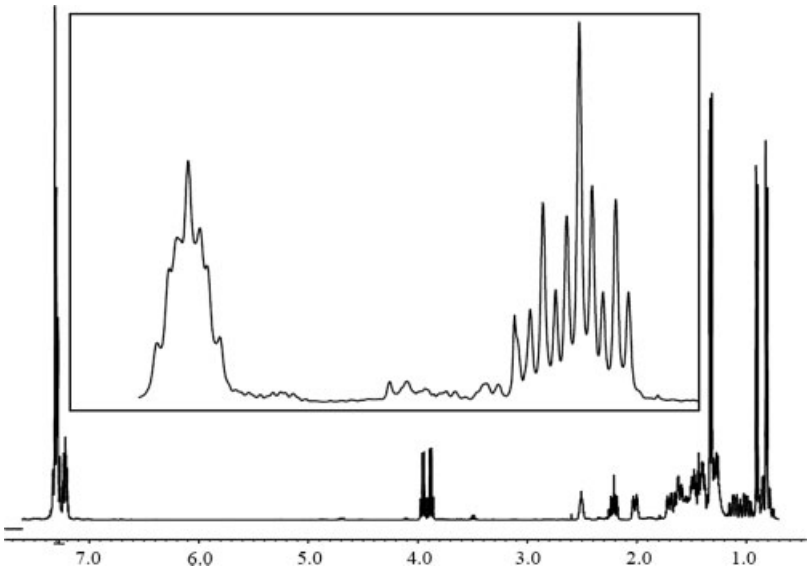

Figure 2. ^{1}H NMR spectrum of **4a**. At the chemical shift positions 3.95 and 3.88 ppm, two quartets were assigned to the CH of the phenylethanamine, and their corresponding CH_3 groups partially overlapped at 1.323 and 1.319 ppm. The methyl groups of the cyclohexane appeared at 0.9 and 0.81 ppm. The expanded view (inset) shows the triple–triple ($^{3}J_{H,H}$ = 3.8 and 5.1) at 2.53 for the *cis* isomer (amine group in the axial position) and the triplet of triplets ($^{3}J_{H,H}$ = 3.9 and 11) at 2.23 for the *trans* isomer (amine group in equatorial position).

axially, as was evident in the resonance of the hydrogen on C1, which was observed as a quintet signal (δ ^{1}H = 2.93, $^{3}J_{H,H}$ = 3.9). A similar observation was made for compound **3d** ($\Delta\delta_H$ = 0.32).

The amines **5a**–**5d** were used as ananchomeric models because these compounds contained a *tert*-butyl group at the C4 equatorial position. The ^{1}H NMR showed evidence that the six-membered ring preferred the chair conformation with the two connectivity isomers (*cis*/*trans*). In general, the vicinal coupling constants 'axial–equatorial' and 'equatorial–equatorial' were almost of the same magnitude, 3.9 and 2.9 ± 0.2 Hz, respectively, whereas the 'axial–axial' constants were 10.8 ± 0.1 Hz. The hydrogen in the equatorial position was high-frequency shifted by 0.4 ppm with respect to the axial hydrogen. Compounds **4a**–**4d** showed a similar coupling pattern, providing evidence for the same preferential conformation with both isomers present; for instance, the ratio between the *cis*/*trans* isomers in compound **4a** was 3 : 1 (Fig. 2).

The chemical shift difference for the hydrogens at C2 and C6 in the ^{1}H NMR spectra permitted assignment of the substituent of the exocyclic amine derivative due to the aromatic ring current effect[7] (Fig. 3). The deshielding effect of the aromatic ring allowed determination of the correct assignment of the C2 or C6 carbons in the cyclohexyl derivative.

Two signals corresponding to the hydrogen atoms at C1 were observed in the ^{1}H NMR spectrum of compound **2a**: one at 1.85 and another at 2.06 ppm, which were expected for the two *trans* diequatorial isomers epimeric at C7 (*ll* and *lu*, respectively), with two different coupling constants, $^{3}J_{Hax-Hax}$ = 10.1 and $^{3}J_{Hax-Heq}$ = 4.2. The corresponding signals of H1 in the *cis* isomers (*ul* and *uu*) appeared at 2.50 and 2.52 ppm, each one with two coupling constants: $^{3}J_{Heq-Heq}$ = 4.2, $^{3}J_{Hax-Heq}$ = 6.7, $^{3}J_{Heq-Heq}$ = 3.7, and $^{3}J_{Hax-Heq}$ = 3.7, respectively. It was possible to identify four doublets at 1.09, 0.98, 0.97, and 0.93 ppm, with coupling constants of 6.4, 7.1, 7.1, and 6.4, respectively, which were assigned to the methyl group in the cyclohexane. The resonances corresponding to H7 were observed at 3.9, 3.9, 3.91, and 4.0 ppm, each with a coupling constant of 6.6 Hz. The compound **2b** had the same

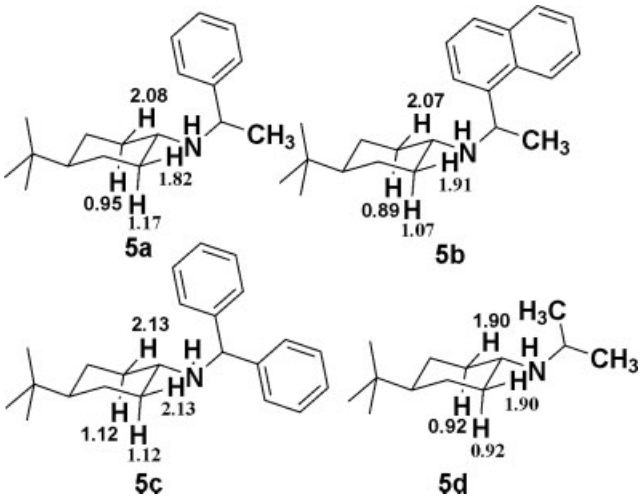

Figure 3. Ananchomeric models (**5a, 5b, 5c,** and **5d**) with a δ_H for the hydrogen atoms α to the amine group, in agreement with the NOESY spectra.

conformation as **2a**. This was confirmed by the chemical shift and coupling constants determined by ^{1}H, ^{13}C, and ^{15}N NMR spectra.

The *trans* isomers of **2c** and **2d** have the two substituents of the cyclohexane in the 'equatorial' positions, as evidenced by the splitting pattern of H1 in the ^{1}H NMR spectra which is observed as a doublet of triplets with two 'axial–axial' and one 'equatorial–axial' spin–spin coupling constants (δ_H = 2.07 and 1.9 for the compound **2c** and **2d**, respectively, $^{3}J_{H,H}$ = 10.0 and 3.7). The *cis* isomers displayed one signal, a doublet–doublet–doublet, with two vicinal coupling constants corresponding to the 'axial–equatorial' interaction and one corresponding to the 'axial–axial' interaction (δ_H = 2.66 and 2.53, for the compounds **2c** and **2d**, respectively; $^{3}J_{H,H}$ = 8.7, 4.3 and 3.9). The ^{1}H NMR spectra of compound **2c** displayed two singlet signals at 5.04 and

Table 2. ^{13}C chemical shifts of the amine series **a** (**1a, 2a, 3a, 4a**, and **5a**)

Compounds	Isomers	1	2	3	4	5	6	7	R = CH3
1a	–	53.62	34.59	25.27	26.22	25.07	33.23	54.46	–
2a	*lu*	61.12	39.39	34.83	26.02	25.88	34.05	56.71	13.43
	ll	59.42	38.44	34.83	26.23	25.74	34.05	54.64	19.57
	ul	54.79	34.31	30.81	22.90	23.42	28.05	54.35	15.44
	uu	55.42	32.40	31.20	21.92	24.44	29.24	54.64	19.87
3a	*RRR*	49.28	32.23	27.06	34.27	20.59	38.49	54.51	21.65
	SRS	53.68	34.15	31.68	34.92	25.08	42.37	54.84	22.78
	RRS	49.28	40.57	26.88	34.27	20.31	29.90	54.44	21.81
	SRR	53.86	43.54	31.95	34.92	25.08	32.96	54.84	22.69
4a	*cis*	50.76	30.52	30.09	32.60	29.79	28.49	54.77	20.83
	trans	53.83	34.63	34.25	32.60	33.97	33.26	54.66	22.43
5a	*cis*	48.46	32.01	21.55	48.28	21.21	29.52	54.92	–
	trans	54.12	34.60	26.29	47.82	26.05	33.15	54.70	–
1b	–	54.06	34.73	25.50	26.36	25.20	33.87	49.73	–
2b	*lu*	61.37	39.33	34.84	26.03	25.86	33.89	51.57	13.51
	ll	59.51	38.76	34.84	26.16	25.56	32.74	50.01	19.80
	ul	55.03	34.52	30.91	23.00	21.85	28.29	49.37	15.52
	uu	55.66	32.03	31.22	21.85	24.53	29.18	50.01	19.93
3b	*RRR*	49.76	32.19	27.05	34.24	20.73	39.08	50.40	21.82
	SRS	54.17	34.34	31.75	34.97	25.24	42.96	49.59	22.78
	RRS	49.53	40.65	27.23	34.24	20.47	30.44	50.25	21.82
	SRR	53.94	43.60	32.07	34.97	24.99	33.55	49.76	22.78
4b	*cis*	51.09	30.61	30.23	32.63	29.95	29.02	50.27	20.95
	trans	54.20	34.61	34.36	32.63	34.08	33.8	49.90	22.46
5b	*cis*	50.47	32.03	21.68	48.27	21.36	30.08	48.78	–
	trans	54.38	34.95	26.41	47.89	26.13	34.12	49.75	–
1c	–	54.08	34.08	25.24	26.37	25.24	34.08	63.79	–
2c	*cis*	55.05	33.52	30.88	23.11	23.33	28.42	63.71	15.14
	trans	59.89	39.26	34.95	26.19	25.78	32.88	64.00	19.96
3c	*cis*	54.23	43.11	31.99	34.49	25.17	34.99	64.05	22.80
	trans	49.70	39.55	26.97	30.66	20.58	33.81	63.66	22.11
4c	*cis*	50.46	34.04	29.67	31.06	29.67	34.04	63.99	21.37
	trans	54.26	34.21	29.87	32.58	29.87	34.21	63.85	22.45
5c	*cis*	48.81	30.85	21.55	48.39	21.55	30.85	64.10	–
	trans	54.69	34.54	26.45	48.03	26.45	34.54	63.97	–
1d	–	53.18	33.88	25.07	25.99	25.07	33.88	44.38	–
2d	*cis*	55.01	32.42	31.26	21.90	24.24	28.79	44.59	13.33
	trans	60.27	38.55	34.76	25.97	25.68	33.54	46.00	19.37
3d	*cis*	53.59	43.19	31.97	33.89	25.12	34.90	44.70	22.65
	trans	48.63	39.68	26.98	31.33	20.29	33.89	44.70	21.39
4d	*cis*	50.57	34.19	29.50	30.24	29.50	34.19	44.73	20.56
	trans	53.62	34.28	29.97	32.59	29.97	34.28	44.86	22.41
5d	*cis*	47.75	30.67	21.23	48.16	21.23	30.67	44.68	–
	trans	53.86	34.21	26.31	47.79	26.31	34.21	44.93	–

tert-butyl group: $\delta_C = 32.53 \pm 0.13$, $\delta_{CH3} = 27.65 \pm 0.08$. $NCCH_3$: $\delta_C = 24.37 \pm 0.75$. In the series **a** phenyl group: $\delta_{Ci} = 146.54 \pm 0.49$, $\delta_{Co} = 126.63 \pm 0.10$, $\delta_{Cm} = 128.12 \pm 1.11$, $\delta_{Cp} = 126.75 \pm 0.07$. In the series **b** naphthyl group: $\delta_{C1} = 142.28 \pm 0.45$, $\delta_{C2} = 129.07 \pm 0.04$, $\delta_{C3} = 125.46 \pm 0.18$, $\delta_{C4} = 127.06 \pm 0.04$, $\delta_{C5} = 123.03 \pm 0.31$, $\delta_{C6} = 125.80 \pm 0.07$, $\delta_{C7} = 125.83 \pm 0.04$, $\delta_{C8} = 123.09 \pm 0.33$, $\delta_{C9} = 134.09 \pm 0.04$, $\delta_{C10} = 131.43 \pm 0.1$. In the **c** phenyl group: $\delta_{Ci} = 144.93 \pm 0.31$, $\delta_{Co} = 126.91 \pm 0.05$, $\delta_{,Cm} = 128.49 \pm 0.04$, $\delta_{Cp} = 127.58 \pm 0.11$.

5.13 ppm corresponding to the hydrogen atom of the exocyclic methine at C7 in each isomer present (*cis* and *trans*, respectively), as well as the doublet signal for the methyl group at $\delta_H = 1.05$ (*cis*) and 1.15 (*trans*) with $^3J_{H,H} = 7.1$ and 6.1, respectively. The *cis*/*trans* ratio was 4 : 1 in compounds **2c** and **2d**.

The isomers of compounds **2a**–**2d**, which included a methyl group on the C2 of the cyclohexane in the *cis* position with respect to the amine group, displayed spectra similar to **5a** due to the average of the coupling constants, as observed in the ^1H NMR spectrum of **4a**. In this compound, the ratio of the amine groups in the axial and equatorial positions of the *cis* isomer was 5 : 1. These data provide evidence that the methyl group preferred the equatorial conformation, as demonstrated by the ^{15}N NMR.

The ^{13}C NMR spectra of the epimers of **3a** and**3b** (1-*R*,3-*R*,7-*R*; 1-*S*,3-*R*,7-*R*; 1-*R*,3-*R*,7-*S*; 1-*S*,3-*R*,7-*S*) were completely different and were assigned by the 1D and 2D spectra, including the ^{13}C–^1H

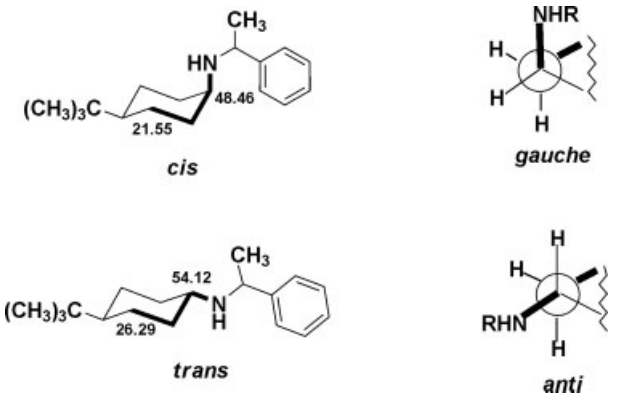

Figure 4. A model of compound **5a** with the data for the cyclohexane C1 and C3 chemical shifts. The Newman projection is shown on the right.

long-range correlation spectrum, which allowed the quaternary carbon assignments.

The ^{13}C NMR spectra (Table 2) showed that the amine group in the equatorial position displayed a C1 chemical shift at higher frequencies compared to the amine group in the axial position. In these compounds, C3 and C5 were shifted by 5 ppm for the case in which the amine group was in the equatorial position (γ_{anti}) compared to the chemical shift when the amine group was in the axial position (γ_{gauche}) (Fig. 4).

The preferred conformation of compound **1a** was the chair, with the amine group in the equatorial position. In addition to the diastereotopic resonances of C2 and C6, which had been previously reported,[8] we found that the C3 and C5 resonances also differed.

The ^{15}N NMR spectrum (Table 3) agreed with the other NMR data.[9] Compounds **1a**–**1d** displayed a preference for the equatorial position ($\delta_N = -309 \pm 3$). In addition, it was observed that $\Delta\delta_{eq-ax} = 9 \pm 3$.

Compound **1a** showed a $\delta_N = -309.1$. This corresponded to the amine group in the equatorial position because two isomers were observed in the ^{15}N NMR spectrum in the compound anchored with the *tert*-butyl group; the *cis* isomer with the amine group in the axial position displayed $\delta_N = -320.9$ and the *trans* isomer with nitrogen in the equatorial position displayed $\delta_N = -309.3$.

In contrast with previous reports,[8,10] the isomers of **2a** preferentially positioned the methyl groups in the equatorial position, as demonstrated by the ^{15}N NMR spectrum, because $\Delta\delta_N = 10.95$ for the *lu* and *uu* isomers. The isomers *ll* and *ul* displayed $\Delta\delta_N = 6.2$. This difference is very narrow to be accepted as evidence for the presence of both the axial and equatorial nitrogen positions. Additional evidence was gathered by preparing the hydrochloride derivatives (labeled in the table as **2 aH$^+$**). These isomers included the ammonium group in the equatorial position and yielded a value of $\Delta\delta_N = 1.8 \pm 0.4$ ppm for the epimers. Formation of the ammonium hydrochloride shifted the peak corresponding to the nitrogen in the equatorial position by 2.9 ppm, whereas the isomers that preferentially positioned the amine group in the axial position presented a difference of 9.7 ± 0.7 ppm due to the change in the conformation.

Conclusions

The assignment of the stereochemistry at each amine center of the compounds examined was enabled by analysis of the mixtures, because mixtures allow the determination of substitution effects. The main conformation of the cyclohexane was the chair; the alkyl groups in the amines were predominantly in the equatorial position. The evidence obtained by ^1H NMR indicated that the substitution effect of the aryl group was larger than that of the methyl groups. In contrast with previous reports, we established that the amine group preferred the equatorial position, including cases in which steric hindrance of the methyl group in the β position was present, as demonstrated by ^{15}N NMR.

Table 3. ^{15}N chemical shifts of the amines

Compounds	Isomers	δ_N	Compounds	Isomers	δ_N
1a	–	−309.09	**1b**	–	−311.91
2a	*lu*	−311.37	**2b**	*lu*	−313.79
	ll	−312.70		*ll*	−315.55
	ul	−318.91		*ul*	−322.3
	uu	−322.32		*uu*	−325.27
3a	*RRR*	−315.70	**3b**	*RRR*	−319.03
	RRS	−316.71		*RRS*	−320.02
	SRR	−307.35		*SRR*	−310.97
	SRS	−307.56		*SRS*	−311.10
4a	*cis*	−315.78	**4b**	*cis*	−318.92
	trans	−308.68		*trans*	−311.54
5a	*cis*	−320.88	**5b**	*cis*	−324.20
	trans	−309.28		*trans*	−311.28
1c	–	−310.53	**1d**	–	−305.45
2c	*cis*	−323.38	**2d**	*cis*	−319.04
	trans	−313.56		*trans*	−309.93
3c	*cis*	−309.33	**3d**	*cis*	−304.91
	trans	−318.51		*trans*	−313.90
4c	*cis*	−318.53	**4d**	*cis*	−313.29
	trans	−310.16		*trans*	−305.52
5c	*cis*	−322.38	**5d**	*cis*	−319.24
	trans	−310.18		*trans*	−305.77
2 aH$^+$	*lu*	−308.54	–	–	–
	ll	−309.80	–	–	–
	ul	−309.95	–	–	–
	uu	−311.95	–	–	–

Experimental

The NMR spectra of compounds **1a**–**5d** were recorded at room temperature ($21 \pm 2\,^\circ C$) using Jeol 270 GSX-Delta (6.345 T), Jeol Eclipse 400 (9.390 T), and Jeol ECA-500 (11.7 T) spectrometers equipped with 5 mm multinuclear probes. All spectra were obtained using natural abundance samples in $CDCl_3$ (0.9 mmol of each compound per 0.4 ml solvent). The unified scale[11] was used as primary reference, the ^1H resonance of TMS in dilute solution (volume fraction, $\varphi < 1\%$) in chloroform. $(CH_3)_4Si$ ($\delta\,^1H = 0$, $\delta\,^{13}C = 0$) and neat CH_3NO_2 ($\delta\,^{15}N$ for $\Xi\,^{15}N = 10.136767$ MHz). The ^1H NMR spectra were recorded at 500 MHz (spectral width: 9384 Hz; acquisition time: 6.984 s, 65536 data points, pulse width 45°, 16 scans, recycle delay: 1 s). $^{13}C\{^1H\}$ NMR spectra were recorded at 100.525 MHz (spectral width: 39.3 kHz; acquisition time: 0.834 s, 32768 data points, pulse width 30°, 256 scans, recycle delay: 1 s). ^{15}N NMR spectra were recorded at 50.7 MHz using a single pulse decoupling experiment with nOe,[12] considering that the $\eta_{max} = -4.93$ with a Waltz-16 composite pulse decoupling

(spectral width: 25406 Hz; 32768 data points, from 1024 to 30 000 scans, depending on the solubility; recycle delay: 1 s).

^{13}C NMR APT spectra were recorded at 67.94 MHz (spectral width: 17006.8 Hz; acquisition time: 0.963 s, 16384 data points, $^{1}J_{C,H} = 145$ using the modulation of J, 1024 scans, recycle delay: 1 s).

^{13}C NMR DEPT spectra were recorded at 100.523 MHz (spectral width: 25 189 Hz; acquisition time: 1.3 s, 32768 data points, setting 90° and 135° versions, $1/(2J_{C,H}) = 3.5$ ms, 512 scans, recycle delay: 2 s).

^{1}H–^{1}H COSY spectra were obtained at 399.78 MHz with the DQF–COSY pulse sequence[12] using a 1024 × 512 data point matrix and a 3299 × 3299 Hz frequency matrix. The recycle delay was 1 s and a total of 16 scans were performed. Fourier transformations were carried out for F1 and F2 using a sine function in the absolute value mode.

^{1}H–^{1}H NOESY[12] spectra were obtained at 399.78 MHz using a 1024 × 512 data point matrix and a 3299 × 3299 Hz frequency matrix. The 1 s mixing time recycle delay was 1 s, and 16 scans were performed. Fourier transformations were carried out for F1 and F2 using a sine function in the absolute value mode.

^{13}C–^{1}H HETCOR spectra[12] were obtained at 100.525 MHz to yield a high resolution in the aliphatic region using a 2048 × 512 data point matrix and a 13 190 × 3299 Hz frequency matrix. The pulse time intervals 1 and 2 were set as $2 \times 1/4J = 1.85$ ms. The recycle delay was 1 s, and 16 scans were performed. Fourier transformations were carried out using a square-sine function for F1 and F2 in the absolute value mode.

The ^{13}C–^{1}H long-range correlation spectrum was recorded at 100.525 MHz with the g-HMBC pulse sequence using a 2048 × 512 data point matrix and 4251 × 20 750 Hz frequency matrix. The delays were set based on the $^{1}J_{C,H} = 140$ Hz and the $^{2/3}J_{C,H} = 8$ Hz. The recycle delay was 1.5 s, and 16 scans were performed. Fourier transformations were carried out using a square-sine function for F1 and F2 in the absolute value mode.

Mass spectrometry (MS) studies of compounds **2a**–**5d** were carried out using a Hewlett-Packard (HP) 5890 spectrometer coupled to a gas chromatograph in the electron ionization (EI) mode (at 70 eV). No mass spectra could be obtained for compounds **1a**–**5a** because of their instability at their respective boiling temperatures.

Melting points were measured using a Mel-Temp 3.0 (Laboratory Device Inc., USA) and are reported without correction. Elemental analyses were performed on a Thermo Finnigan Flash 1112. Mass spectra were obtained by electronic ionization at 70 eV in an HP-5989 spectrometer.

Preparation

The imines were obtained according to previous reports[13] by the condensation of equimolar amounts of the corresponding amines and cyclohexanones in pentane or toluene solutions. The reactions were carried out under reflux (for 12 h) in a Dean–Stark water separator. The compounds were purified by low-pressure distillation. The imine groups were reduced by $NaBH_4$, as previously described[14]; the reactants were dissolved in methanol at room temperature (26 ± 3 °C), equilibrated for 96 h, and the pH of each solution was adjusted to 1 using HCl. The compounds were washed with an aqueous alkaline solution (NaOH, pH = 11) and extracted with CH_2Cl_2 at neutral pH. The solutions were evaporated to dryness under vacuum and purified by column chromatography (ethylacetate/hexane 9 : 1, silica gel). The physical and spectroscopic properties of the amines **1a**,[1c,4a,8,15b] **2a**,[8,10,15c] **3a**,[1a,b,15a] **4a**,[15a] **5a**,[15e] **1b**,[2] **1d**,[3] **2d**,[15f] and **5d**[15d,e] were in good agreement with previous reports.

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