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Stereochemical analysis of *N*-cyclohexylidene-*N*-(1-phenylethyl)amine derivatives

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The configurational properties of a series of cyclohexylidene imines are discussed on the basis of their ^{1}H, ^{13}C and ^{15}N NMR spectral data. Copyright © 2005 John Wiley & Sons, Ltd.

KEYWORDS: ^{1}H NMR; ^{13}C NMR; ^{15}N NMR; configuration; *N*-cyclohexylidene-1-phenylethylamine derivatives

INTRODUCTION

Imines are important intermediates which have been used in deracemizing alkylation,[1] acylation,[2] lactams and oxaziridine preparations[3] as well as in Michael additions.[4] Iminium salts have also been proposed as intermediates in the preparation of amines obtained by reductive amination of ketones with reducing agents,[5] but this intermediate has never been detected nor isolated. Eventhough imines have been widely used for the last 20 years their structures have not been completely analyzed by means of spectroscopic methods. To our knowledge, only the absolute configurations of *N*-cyclohexylidene-1-phenylethylamine (**1**) and some isomers of *N*-(2-methylcyclohexylidene)-1-phenylethylamine (**2**) prepared by stereoselective alkylation, have been determined by means of chiroptical methods[6] and their relative configuration established by NMR.[7]

In this paper we report the ^{1}H, ^{13}C and ^{15}N NMR assignment of imines **1**–**5** (Scheme 1). Although the structures of these compounds have been described as simple, they possess some symmetry elements that require more detailed analysis.[8]

RESULTS AND DISCUSSION

Stereochemical analysis

First, the chiral center C-7 produces a pair of enantiomers. Secondly, The C═N double bond gives rise to two diastereomers (*E* and *Z*) which can easily be differentiated by NMR methods if the cyclohexane ring is conformationally fixed. In **1**, the cyclohexane ring can undergo ring inversion by which these *E*/*Z* diastereomers interconvert. Therefore, only one signal set is observed for this compound at room temperature, whereas coalescence is observed on lowering the temperature; two signal sets appear at 203 K (see also footnote a of Table 2); $\Delta G_c^* = 46.9 \pm 1.2$ kJ mol^{-1}.

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In contrast, the four-substituted derivatives **4** and **5** are conformationally fixed because the methyl and the *tert*-butyl group, respectively, strongly prefer the equatorial position (steric anchor). Thereby, the interconversion of the *E*/*Z* diastereomers is blocked and two diastereomeric pairs of enantiomers exist permanently. As a consequence, two NMR signal sets are observed for each compound.

In each of the imines **2** and **3**, a new stereogenic center is introduced (C-2 and C-3, respectively) giving rise to four diastereomeric pairs of enantiomers so that four signal sets emerge. In order to assign the configurations of compound **3** with its equatorial methyl group, (*R*)-3-methylcyclohexanone as well as optically pure (*R*)- or (*S*)-1-phenylethylamine were used as precursors.

It was not possible to assign compound **2** with the strategy used for **3** because 2-methylcyclohexanone has a tautomeric ketone-enol equilibrium that restrains working with optically pure compounds. However, Fraser *et al*. prepared the isomers *Z* of imine **2** by stereoselective methylation via optically active lithioenamine.[1b] They elucidated their structure and found that the methyl group of cyclohexane occupies the axial position. In our observations, the assignment is in agreement to their report[1b] with the difference that the *E* isomers with less hindrance are the most abundant (9 : 1 ratio).

NMR spectra

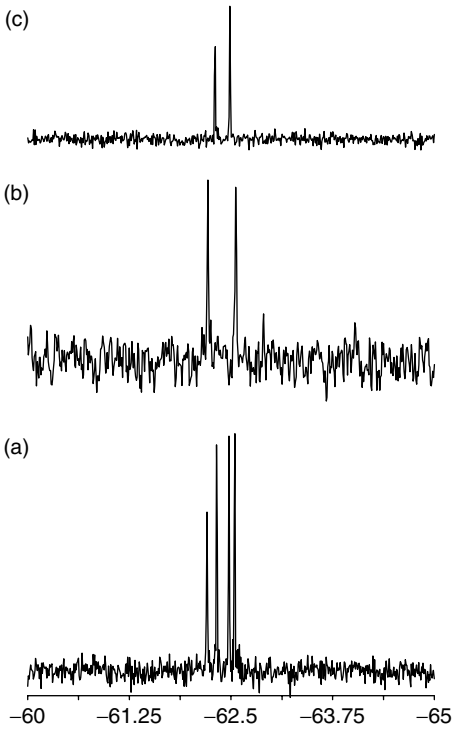
We describe herein our investigations concerning the NMR spectral analysis of cyclohexylidene derivatives **1**–**5**. The compounds were prepared by reaction of 2-methyl, 3-methyl, 4-methyl and 4-*tert*-butylcyclohexanoens with 1-phenylethylamine (both racemic and optically pure samples). Detailed spectral analysis presents a great challenge due to the complexity of the ^{1}H NMR spectra (Table 1) of the cyclohexyl fragment and the similarity of many of the chemical shift both in ^{1}H and ^{13}C NMR for the isomers. Only, it is possible to distinguish a doubled triplet signal for

the axial H-2 in **3** to **5** which has a vicinal coupling of 4.5 Hz (axial with equatorial protons) as well as a geminal plus a vicinal coupling (axial with axial proton) of 13 Hz each. This proves the chair conformation.

The atomic connectivity was established by heteronuclear and homonuclear correlation spectroscopy (COSY and $^{13}C-^{1}H$ HETCOR). ^{15}N NMR spectra were recorded using a single pulse ^{1}H-decoupled experiment (no NOE). The ^{13}C and ^{15}N NMR reveal systematic substituent effects which support the signal assignment.

The assignment of the configuration originated by the double bond (*E*, *Z*) is based on ^{13}C NMR data (Table 2). The 1-phenylethylamine substituent induces a diamagnetic γ effect at the carbon in *Z*-position shifting its signal by 10 ppm to low frequency compared to the *E*-positioned carbon. The introduction of a methyl group gives rise to a deshielding of α carbons by 6.5 ± 0.5 ppm (C-3 and C4 for imine **3** and **4**, respectively); its effect for β carbons is 8.0 ± 0.5 ppm deshielding. In contrast, the methyl effect on C-2 in compound **2** is only +2 to +4 ppm; the γ bond effect is less than 1.2 ppm. The *tert*-butyl group shifts the α signal (C-4) by +22 ppm and its β effect is less than +2 ppm. This assignment is in agreement with previous reports.[7,8,10]

The ^{15}N NMR chemical shifts (Table 3) reflect a dependence on the configuration of the molecules; however, the shift difference between isomers is less than 0.4 ppm (Scheme 2). In derivative **2**, only the signals for the main isomers product were observed.



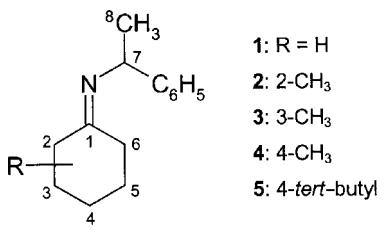
Scheme 2. ^{15}N NMR spectra of **3**; (a) spectrum of the diastereomeric mixture, (b) *E* and *Z* isomers of the (3*R*,7*R*)-ketimine **3**, and (c) *E* and *Z* isomers of the (3*R*,7*S*)-ketimine **3**.

EXPERIMENTAL

The NMR spectra were recorded at room temperature with a Jeol eclipse +400, equipped with a 5-mm multinuclear autotuning probe and a variable temperature unit using 5-mm od tubes. The chemical shifts are referenced to internal Me_4Si [$\delta(^1H)$ and $\delta(^{13}C)$ 0 ppm] and neat $MeNO_2$ [$\delta(^{15}N)$ 0 ppm for $\Xi(^{15}N) = 10.136\,767$ MHz]. $CDCl_3$ solutions containing 0.8 mmol of the samples in natural abundance were used for ^{13}C and ^{15}N NMR experiments while ^{1}H data were determined using 20 mg in 0.7 ml.

^{1}H NMR spectra were recorded at 399.65 MHz (spectral width 3915.4 Hz, acquisition time 4.2 s, 16 384 data points, equivalent 45° pulse duration, 16 scans, recycle delay 3 s).

$^{13}C\{^{1}H\}$ NMR spectra were recorded at 100.53 MHz, spectral width 25 181 Hz, 32 768 data points, recycle delay of 0.8 s, 32 scans. Similar conditions were used for APT and INEPT spectra[11]. $^{13}C^{1}H$ NMR spectra of **1** were recorded at low temperature as well and the coalescence temperature T_C was determined for the carbon para of phenyl group.



1: R = H
2: 2-CH_3
3: 3-CH_3
4: 4-CH_3
5: 4-*tert*-butyl

Scheme 1. Structures of the imines **1**–**5**.

$^{15}N\{^{1}H\}$ NMR spectra were obtained at 40.51 MHz using a single pulse ^{1}H-decoupled without NOE method[11], spectral width was 16 216 Hz, 16 384 data points 2024 scans, recycle delay 2 s.

H,H–COSY spectra were obtained with the dqf-COSY pulse sequence[11] using a 1024×512 data point matrix and a 3522.4×3522.4 Hz, the recycle delay was 1 s. Fourier transformations were carried out using a sine-bell function for F1 and F2, in the absolute value mode.

The $^{13}C,^{1}H$–COSY spectra[11] were obtained for the aliphatic region using a 1024×512 data point matrix and a 5026×1958 Hz frequency matrix, pulse time intervals 1 and 2 were set as $2 \times 1/4J = 1.85$ ms, respectively, and recycle delay was 1 s. Fourier transformations were carried out using a sine-bell function for F1 and F2, in the absolute value mode.

The MS were determined in a Hewlett-Packard 5890 spectrometer coupled with a gas chromatograph in electron ionization mode (EI).

The Schiff bases were prepared from the corresponding cyclohexanones and 1-phenylethylamine in toluene solution at reflux for 24 h in a Dean-Stark water separator. Both the cyclohexanones and the amines are commercially available products. The physical and spectroscopic properties are in good agreement with previous reports: **1**,[6,7] **2**,[7] **3**,[12] **4**,[12c] **5**.[3a]

N-[3-methylcyclohexylidene]-1-phenylethylamine (**3**) was prepared from (*R*)-(+)-3-methylcyclohexanone and the optically pure (*R*)- or (*S*)-1-phenylethylamine as well as the racemic mixtures of both. We used (*R*)- or (*S*)-1-phenylethylamine for the preparation of compounds **4** and **5**

Table 1. ^{1}H NMR of the imines **1–5**

		2				**3**							
		Major		Minor						**4**		**5**	
H-	**1**	*E*-2*S**,7*R**	*E*-2*S**,7*S**	*Z*-2*S**,7*R**	*Z*-2*S**,7*S**	*E*-3*R*,7*R*	*E*-3*R*,7*S*	*Z*-3*R*,7*R*	*Z*-3*R*,7*S*				
2	2.34 m	2.41 m	2.41 m	3.08 m	3.19 m	1.93 m	1.88 m	1.56 m	1.65 m	2.39 m	2.44 m	2.50 m	2.50 m
						2.19 dt	2.19 dt	2.77 m	2.69 m	2.16 dt	2.22 dt	2.24 dt	2.20 dt
						(5.1, 12.8)	(5.1, 12.8)			(3.8, 13.2)	(4.6, 12.8)	(4.7, 13.1)	(4.7, 13.1)
3	1.71 m	1.91 m	1.41 m	1.56 m	1.72 m	1.2 m	1.20 m	1.65 m	1.4 m	1.69 m	1.84 m	2.90 m	2.90 m
										0.83 m	1.24 m	0.85 m	0.85 m
4	1.57 m	1.42 m	1.68 m	1.48 m	1.50 m	1.42 m	1.54 m	1.54 m	1.38 m	1.66 m	1.66 m	1.29 m	1.29 m
						1.78 m	1.80 m	1.80 m	1.80 m				
5	1.55 m	1.68 m	1.52 m	1.66 m	1.38 m	1.18 m	1.16 m	1.20 m	1.16 m	1.76 m	1.84 m	1.96 m	1.96 m
						1.78 m	1.71 m	1.77 m	1.71 m	1.13 m	1.24 m	2.23 m	2.23 m
6	2.30 m	1.99 m	2.64 m	2.32 m	1.59 m	1.68 m	188 m	2.15 dt	2.15 dt	2.74 m	2.74 m	2.88 m	2.88 m
						2.81 m	2.70 m	(4.8, 12.8)	(4.8, 12.8)	1.74 m	1.74 m	1.68 dt	1.68 dt
								2.32 m	2.32 m			(4.9, 13.7)	(4.9, 13.7)
7	4.68	4.70	4.70	4.80	4.80	4.73	4.69	4.70	4.69	4.81	4.82	4.69	4.70
	q (6.6)	q (6.7)	q (6.7)	q (6.9)	q (6.9)	q (6.6)	q (6.6)	q (6.6)	q (6.6)	q (6.9)	q (6.9)	q (6.6)	q (6.6)
8	1.44	1.38	1.40	1.48	1.45	1.47	1.46	1.46	1.46	1.47	1.45	1.45	1.48
	d (6.6)	d (6.7)	d (6.7)	d (6.9)	d (6.9)	d (6.6)	d (6.6)	d (6.6)	d (6.6)	d (6.9)	d (6.9)	d (6.6)	d (6.6)
H_o	7.33	7.43	7.43	7.46	7.46	7.33	7.33	7.41	7.41	7.34	7.33	7.36	7.34
	d (7.0)	d (7.3)	d (7.3)	d (7.3)	d (7.3)	d (7.0)	d (7.0)	d (7.0)	d (7.0)	dd (7.2, 1.5)	dd (7.2, 1.5)	dd (7.6, 1.5)	dd (7.8, 0.8)
H_m	7.25	7.33	7.33	7.33	7.33	7.29	7.26	7.29	7.26	7.29	7.24	7.30	7.28
	t (7.0)	t (7.3)	t (7.3)	t (7.3)	t (7.3)	t (7.0)	t (6.9)	t (7.0)	t (6.9)	t (7.2)	t (7.2)	t (7.6)	t (7.8)
H_p	7.14	7.22	7.22	7.22	7.22	7.18	7.15	7.18	7.15	7.16 tt	7.11 tt	7.19	7.17
	t (7.0)	t (7.3)	t (7.3)	t (7.3)	t (7.3)	t (7.0)	t (6.9)	t (7.0)	t (6.9)	(7.2, 1.5)	(7.2, 1.5)	m	m
R	–	1.13	1.08	0.88	1.13[a]	0.96	0.96	0.95	0.90	0.95	0.88	0.89	0.83
		d (6.7)	d (6.7)	d (7.4)		d (6.2)	d (5.8)	d (5.9)	d (6.6)	d (6.5)	d (6.4)	s	s

*R** and *S** are relative configurational descriptors.[9] m = multiplet, q = quartet, t = triplet, d = doublet, s = singlet; *J*-values (Hz) in parentheses.

[a] Overlapped.

Table 2. ^{13}C NMR chemical shift of the imines **1–5**

		2											
		Major		Minor[b]		**3**							
C-	**1**[a,b]	*E*-2*S**,7*R**	*E*-2*S**,7*S**	*Z*-2*S**,7*R**	*Z*-2*S**,7*S**	*E*-3*R*,7*R*	*E*-3*R*,7*S*	*Z*-3*R*,7*R*	*Z*-3*R*,7*S*	**4**		**5**	
1	171.97	173.45	173.76	175.93	175.38	171.87	172.04	171.54	171.81	171.72	171.52	172.42	172.21
2	40.13	42.38	42.38	31.59	31.87	48.50	48.43	37.48	37.61	39.08	39.05	39.75	39.71
3	27.72	36.08	35.96	32.78	33.33	34.56	34.59	34.08	33.43	35.56	35.53	29.02	28.97
4	25.97	24.50	24.62	20.47	20.37	26.15	26.38	26.38	25.68	31.94	31.90	47.72	47.64
5	27.00	27.92	27.92	27.46	27.46	34.60	34.47	34.47	34.47	34.55	34.51	28.34	28.31
6	29.40	28.20	28.26	35.77	36.30	28.21	28.93	39.77	39.72	28.19	28.19	32.45	32.16
7	57.64	57.57	57.66	57.14	57.14	58.25	58.17	58.44	58.33	57.76	57.63	58.01	57.85
8	24.99	25.81	25.66	25.44	25.44	25.59	24.87	25.71	24.95	25.06	24.72	25.30	24.95
C_i	146.24	147.26	147.17	146.53	146.53	146.48	146.48	146.20	146.26	146.21	145.95	146.53	146.21
C_o	126.61	126.84	126.72	126.85	126.36	126.57	126.57	126.52	126.54	126.65	126.59	126.61	126.57
C_m	128.18	128.31	128.31	128.47	128.47	128.44	128.44	128.30	128.30	128.35	128.35	128.33	128.33
C_p	126.43	126.36	126.30	126.92	125.80	126.39	126.39	126.33	126.38	126.43	126.43	126.40	126.38
R	–	17.65	17.56	16.86	17.50	22.06	22.02	22.68	22.59	21.28	21.17	27.62	27.57

[a] At 203 K: $\delta(C_o)$ 127.09, 126.90 ppm; $\delta(C_m)$ 128.47, 128.26 ppm, $\delta(C_p)$ 126.62, 126.43 ppm.

[b] The chemical shift data for **1** and the *Z*-2*S**,7*R** and *Z*-2*S**,7*S** isomers of **2** are in agreement with Ref. 7.

Table 3. ^{15}N NMR chemical shifts of the imines 1–5

		$\delta(^{15}N)$
1		−63.3
2	*E*-2*S**,7*R**	−60.8
	E-2*S**,7*S**	−60.6
	E-3*R*,7*R*	−62.2
3	*E*-3*R*,7*S*	−62.3
	Z-3*R*,7*R*	−62.5
	Z-3*R*,7*S*	−62.5
4		−62.3
		−62.4
5		−64.1
		−64.3

as well; both products showed NMR spectra identical with the one prepared from the racemic mixture.

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