Carbon-13 Nuclear Magnetic Resonance Spectra of Phencyclidine Analogs Substituted in the Piperidine and Aromatic Rings

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Natural abundance carbon-13 chemical shifts are reported for the hydrochloride salts of phencyclidine (**1a**) and twelve analogs substituted in the piperidine and aromatic rings. The signals are assigned on the basis of chemical shift theory, SFORD multiplicities, signal intensities, and comparisons with related compounds.

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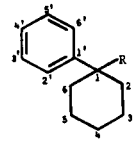
The dissociative anesthetic phencyclidine (**1a**) is a highly potent and widely abused drug [1]. Moreover, numerous phencyclidine analogs have been prepared, several of which have similar biological activities [2]. Consequently, the study of the natural abundance ^{13}C nmr spectra of phencyclidine (**1a**) and its analogs is of interest from both a conformational and a forensic viewpoint. Not surprisingly, several ^{13}C nmr papers have appeared since the initial report by Geneste and Kamenka [3]. We reported the carbon-13 chemical shifts for the hydrochloride salts of phencyclidine (**1a**) and sixteen analogs [4]. Subsequently, Bailey and Legault [5] described essentially identical assignments for eleven of these compounds, emphasizing the identification and authentication of forensic samples. Continuing their earlier conformational study, Geneste and co-workers [6] reported some carbon-13 chemical shifts for a series of methylcyclohexyl analogs of phencyclidine (**1a**).

Chart I



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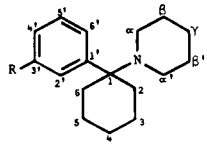
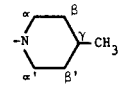
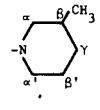
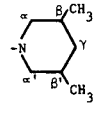
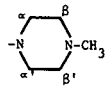
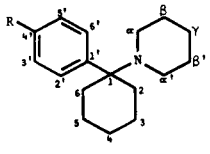


2

Compound	R
a	
b	
c	
d	
e	

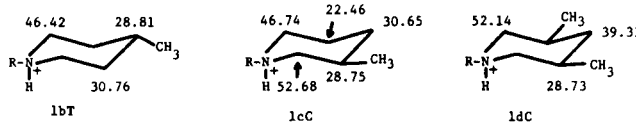
Compound	R
a	OCH_3
b	CH_3
c	NO_2
d	NH_2
e	OH



3

Compound	R
a	OCH_3
b	CH_3
c	NO_2

Chart II



R = 1-phenylcyclohexyl

The designations C (cis) and T (trans) are used to denote the relationship of the methyl group(s) relative to the R group.

In this paper we report the carbon-13 chemical shifts of an additional twelve phencyclidine analogs substituted in the piperidine and aromatic rings. The compounds examined in the present study are summarized in Chart I. The ^{13}C nmr spectra were obtained on the hydrochloride salts under conditions described in the Experimental section. Signal assignments were made on the basis of ^{13}C nmr chemical shift theory, multiplicities as obtained by single-frequency off-resonance decoupling (SFORD) experiments, signal intensities, and comparisons to structurally related compounds. The chemical shift assignments are summarized in Tables I and II.

Discussion.

Analogs **1b-e** and **3a-b** were prepared by standard procedures [2] as described in the Experimental. Nitration of phencyclidine (**1a**) as described by Kalir and co-workers [7] provided compounds **2c** and **3c**. In accordance with more recent reports [8,9] on the nitration of **1a**, we found the expected *meta* isomer **2c** to be the principal product [10]. Johnson and co-workers [9] reported that **2c** could be converted to **2d** by hydrogenation using a 5% palladium/-carbon catalyst or by sodium sulfide reduction. We observed that **2c** could also be conveniently converted to **2d** using 85% hydrazine in the presence of 10% palladium/-carbon. In accordance with Johnson and co-workers [9] but in contrast to an earlier report [6], we found that attempts to reduce **3c** to the corresponding aniline under a variety of conditions resulted in loss of piperidine to give 4-(1-cyclohexenyl)aniline. Analog **2e** was derived from **2d** by diazotization and diazonium salt decomposition. Com-

Table I

Carbon-13 Nuclear Magnetic Resonance Chemical Shifts of Phencyclidine Hydrochloride and Its Analogs Substituted in the Piperidine Ring [a]

Compound Carbon	**1a**	**1b**	**1c**	**1d**	**1e**
1′	130.11	130.11	130.06	130.11	129.43
2′, 6′ [b]	129.18 [c]	129.18 [c]	129.28	129.18	129.23
3′, 5′ [b]	128.84	128.84	128.89	128.89	128.65
4′	129.18 [c]	129.18 [c]	129.18	129.33	129.82
1	70.77	70.57	70.81	70.91	72.23
2, 6 [b]	30.29	30.39 [d]	30.44 [e] 30.34 [e]	30.54	30.05
3, 5 [b]	22.59 [e]	22.44	22.44	22.49	22.25
4	24.30	24.30	24.30	24.34	24.34
α, α′ [b]	46.82	46.48	(α) 52.43 (α′) 46.24	51.99	42.78
β, β′ [b]	22.44 [e]	30.39 [d]	(β) 28.25 (β′) 22.20	27.81	49.65
γ	22.40	29.37	30.83 [e]	39.70	—
C-CH_3	—	20.49	19.08	18.88 [b]	—
N-CH_3	—	—	—	—	42.14

[a] The spectra were run in deuteriochloroform solution. [b] Unless otherwise indicated, the resonances for these carbons were twice as intense as other similar resonances. [c] These resonances were three times as intense as other similar resonances. [d] These resonances were four times as intense as other similar resonances. [e] Assignments in any one column may be interchanged.

Table II

Carbon-13 Nuclear Magnetic Resonance Chemical Shifts of Phencyclidine Hydrochloride and Its Analogs Substituted in the Aromatic Ring [a]

Compound Carbon	**1a**	**2a**	**2b**	**2c**	**2d**	**2e**	**3a**	**3b**	**3c**
1′	130.60	132.40	130.50	133.13	133.72	132.01	122.31	127.67	138.25
2′	129.82 [b]	114.02	130.35 [e]	124.26 [e]	123.82 [e]	116.85 [e]	131.33	129.77 [e]	131.81
3′	128.79 [b]	159.61	138.11	148.54	132.35	157.90	114.07	129.48 [e]	123.63
4′	129.18	116.31	129.82 [e]	124.65 [e]	124.65 [e]	116.21 [e]	159.51	138.74	147.76
5′	128.79 [b]	129.87	128.60	130.45	128.84	129.67	114.07	129.48 [e]	123.63
6′	129.82 [b]	121.92	126.94	136.79	130.16	120.21	131.33	129.77 [e]	131.81
1	70.23	70.23	70.18	69.65	69.99	70.23	70.08	70.13	69.69
2, 6 [b]	29.76	29.91	29.81	29.66	29.95	30.10	30.00	30.00	29.76
3, 5 [b]	22.44 [d]	22.54 [d]	22.49 [d]	22.44 [e]	22.59 [e]	22.64 [d]	22.49 [d]	22.49 [d]	22.49 [e]
4	24.59	24.59	24.64	24.59	24.59	24.59	24.69	24.69	24.54
α, α′ [b]	46.78	46.97	46.78	46.87	47.02	46.92	46.58	46.78	47.02
β, β′ [b]	22.44 [d]	22.54 [d]	22.49 [d]	22.25 [e]	22.44 [e]	22.64 [d]	22.49 [d]	22.49 [d]	22.44 [e]
γ	21.86	21.91	21.96	21.71	21.86	21.96	21.96	21.91	21.66
C-CH_3	—	—	21.27	—	—	—	—	20.64	—
O-CH_3	—	55.31	—	—	—	—	55.21	—	—

[a] The spectra were run in dimethylsulfoxide-d_6 solution. [b]-[e] Notes to Table I.

pound **2e** was also obtained by boron tribromide *O*-demethylation [11] of **2a**. However, an attempted boron tribromide *O*-demethylation of **3a** provided only 4-(1-cyclohexenyl)phenyl, the same product obtained from treatment of **3a** with hydrobromic acid [7].

The assignment of the ^{13}C nmr chemical shifts of phencyclidine (**1a**) hydrochloride has been detailed in earlier papers [3-5]. In the present study, the aromatic and cyclohexyl carbon resonances of the piperidine ring substituted analogs were easily assigned by their intensities and SFORD multiplicities and by comparison to the corresponding phencyclidine (**1a**) hydrochloride resonances (see Table I). A small chemical shift difference was noted between C-2 and C-6 of the β-methyl analog **1c**. This was attributed to chemical shift nonequivalence induced by the asymmetric carbon [12].

Table III

Melting Point and Analytical Data on the Phencyclidine Analogs

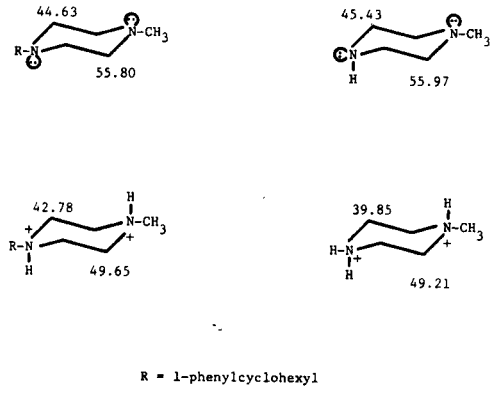
Compound No.	Molecular Formula	Mp °C [a]	Literature Mp °C (Reference)	Analysis % [b] Calculated C	H	N	Found C	H	N
1b	$C_{18}H_{28}ClN$	204-205	215-216 [2b]	73.57	9.60	4.77	73.34	9.48	4.66
1c	$C_{18}H_{28}ClN$	203-204	210-211 [2b]	73.57	9.60	4.77	73.38	9.66	4.62
1d	$C_{19}H_{30}ClN$	209-211		74.12	9.82	4.55	73.92	9.74	4.42
1e	$C_{17}H_{26}N_2$ [c]	69-70	69-70 [2a]						
2a	$C_{18}H_{28}ClNO$	196-197	206-207 [6]	69.77	9.11	4.52	70.03	9.02	4.32
2b	$C_{18}H_{28}ClN$	217		73.57	9.60	4.77	73.35	9.60	4.69
2c	$C_{17}H_{25}ClN_2O_2$	219-220	215-216 [9]	62.85	7.76	8.62	63.13	7.76	8.50
2d	$C_{17}H_{26}N_2$ [c]	124-125.5	124-125 [6]						
2e	$C_{17}H_{26}ClNO \cdot \frac{1}{4}H_2O$ [d]	190.5-192		67.98	8.89	4.66	67.64	9.25	4.40
3a	$C_{18}H_{28}ClNO$	177-178.5, 230-232 [e]	186-187 [2b] 245 [2a] 183 [23]	69.77	9.11	4.52	69.72	9.21	4.47
3b	$C_{18}H_{28}ClN$	208-210, 239-242 [e]	136-137 [2b] 217 [23]	73.57	9.60	4.77	73.36	9.56	4.61
3c	$C_{17}H_{25}ClN_2O_2$	234-238	237-238 [9]						

[a] All melting points were obtained on a Hoover capillary apparatus. [b] Elemental analyses were not obtained on those analogs whose melting points corresponded closely to reported values. [c] Free bases. [d] The sample analyzed for ¼ H_2O before and after vacuum drying at 100° overnight. [e] The sample melted sharply at the lower temperature. The melt resolidified. Upon continued heating, the resolidified sample gradually darkened and finally decomposed at the higher temperature.

In the case of the heterocyclic ring, the C-methyl and *N*-methyl resonancces of analogs **1b-e** were distinguished by their appearance as quartets in the off-resonance spectra. Likewise, the methine carbons of compounds **1b-d** stood out as SFORD doublets. The remaining methylene carbon resonances of **1b-d** were assigned by comparison of the observed chemical shifts with values calculated from the corresponding carbons of phencyclidine (**1a**) hydrochloride using $\Delta\delta$ values derived from chemical shift data on similarly substituted *N*-methylpiperidinium hydrochloride salts reported by Eliel and co-workers [13]. To make these calculations, we assumed that the conformers illustrated in Chart II were the predominant solution conformers of **1b-d** [14]. This assumption was reasonable since these were the predominant conformers for the similarly substituted *N*-methylpiperididium hydrochloride salts [13]. In addition, since only one resonance was observed for each piperidine carbon, conversion between conformers was rapid on the nmr time scale. Using the calculated values for conformers **1bT**, **1cC** and **1dC**, we assigned the remaining methylene carbon resonances of **1b-d** as shown in Table I. The agreement between the observed and calculated values ranged from 0.08 ppm to 0.92 ppm. The discrepancies may be due in part to solvent differences, since the chemical shifts of the model compounds were measured in deuterium oxide [13], and in part to additional substituent effects due to the bulky 1-phenylcyclohexyl group [15].

The C-α,α' and C-β,β' resonances of analog **1e** were assigned by comparison to the corresponding chemical shifts

Chart III

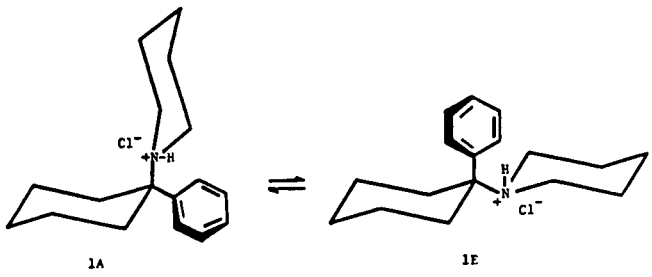


R = 1-phenylcyclohexyl

of *N*-methylpiperazine as illustrated in Chart III. Our chemical shift values for *N*-methylpiperazine base were in excellent agreement with those reported by Ellis and Jones [16]. In the case of the dihydrochloride salts, the C-α,α' resonance of analog **1e** underwent a smaller upfield protonation shift than the corresponding *N*-methylpiperazine signal. We attributed this to the difference between axial protonation of the tertiary amine nitrogen (**1e**) and equatorial protonation of the secondary amine nitrogen of *N*-methylpiperazine. A similar difference in protonation effects was observed for piperidine and *N*-methylpiperidine [17].

The signals due to the cyclohexyl and piperidine carbon resonances of the aromatic ring substituted analogs were differentiated by their intensities and SFORD multiplicities and by comparison to the corresponding phencyclid-

Chart IV



1A 1E

ine (**1a**) hydrochloride resonances (*cf.* Table II). As before, the *C*-methyl and *O*-methyl resonances were distinguished by their off-resonance quartets, while the substituted aromatic carbons gave off-resonance singlets. To assign the remaining aromatic carbon signals, we compared the observed chemical shifts with values calculated from the corresponding carbons of phencyclidine (**1a**) hydrochloride using the aromatic substituent parameters reported by Levy and co-workers [18]. The agreement between the observed and calculated values was sufficiently close to permit the assignments shown in Table II. In the case of analogs **2a-e**, the C-2′ and C-4′ resonances were further distinguished on the basis of signal intensities with the more intense signal being assigned to C-4′. Due to the position of C-4′ on the aromatic molecular axis of preferred rotation [19], we expected it to have a shorted relaxation time and thus a more intense signal under the conditions of rapid rotation. Our assignments for the nitro compounds **2c** and **3c** were in good agreement with previously reported values [8].

In our previous report [4], we noted that the chemical shift of the cyclohexane C-3,5 resonance remained reasonably consistent (22.24 ± 0.81 ppm) over the entire series of compounds. This observation suggested that the predominant solution conformation of the phencyclidine analogs was similar to **1E** (*cf.* Chart IV); **i.e.**, the amino substituent occupied the equatorial position. The twelve analogs examined in the present study were assumed to exhibit a similar solution behavior, and the assignments reported in Tables I and II support this assumption [20]. Further evidence that **1E** is the conformation responsible for the biological activity of the phencyclidine analogs has been obtained from *in vivo* rotarod testing [6] and *in vitro* binding experiments on a specific receptor in rat brain membranes [21].

EXPERIMENTAL

Chemicals.

A sample of phencyclidine (**1a**) hydrochloride was obtained from Philips Roxane, Inc., St. Joseph, Missouri, through the courtesy of the National Institute on Drug Abuse. Analogs **1b-e**, **2a-b** and **3a-b** were synthesized from the appropriate carbonitrile intermediates [2a] using the Grignard procedures described by Maddox and co-workers [2b]. In the case of **3a**, it was necessary to use 1,2-dibromoethane to initiate formation of the Grignard reagent. Nitration of phencyclidine (**1a**) after the procedure of Kalir and co-workers [7] provided a 4:1 mixture of **2c** and **3c** which was separated by fractional crystallization [7,8]. Treatment of **2c** with 85% hydrazine in the presence of 10% palladium/carbon [22] provided **2d** in 70% yield. A sample of **2d** was converted to **2e** *via* the diazonium salt [7]. All the analogs except **1e** and **2d** were purified as the hydrochloride salts and all were characterized by melting point and spectral data. Due to the hygroscopic nature of the dihydrochloride salts, analogs **1e** and **2d** were purified as the free bases and were converted to the salts just prior to spectral analysis. The melting point and analytical data on the analogs are summarized in Table III. Elemental analyses were performed by Micro-Tech Laboratories, Inc., Skokie, Illinois.

Spectral Measurements.

The natural abundance ^{13}C nmr spectra were determined at 25.034 MHz on a modified JEOL JNM-PS-100 FT nmr interfaced with a Nicolet 1085 20K Fourier-transform computer system. Interferograms were stored in 8K of computer memory, which allowed 4K output data points in the Fourier-transformed, phase corrected real spectrum. Proton lines were decoupled by a broad band (2500 Hz) irradiation from an incoherent 99.539 MHz source. A flip angle of 72°, fixed pulse repetition time of 0.90 second, and a spectral width of 5000 Hz were used. Typically, 1012 data accumulations were obtained for 25-30 mg of sample in 0.3 ml of solvent; twice as many accumulations were taken for SFORD spectra. Samples were run at the ambient temperature in 5 mm o.d. tubes, using the deuterium resonance of the solvent as an internal lock. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane and are believed to be precise to within ±0.05 ppm. Whereever possible, spectra were recorded in both deuteriochloroform and dimethylsulfoxide-d_6 [24], and the chemical shift data obtained for the deuteriochloroform solutions agreed closely with that obtained in dimethylsulfoxide-d_6 solution.

Acknowledgement.

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[14] The conformers illustrated in Chart II show the bulky 1-phenylcyclohexyl group occupying an equatorial position with respect to the piperidine ring. This is the case for phencyclidine hydrochloride in solution [3,4] and in the solid state; see P. Argos, R. E. Barr and A. H. Weber, *Acta Cryst.*, **B26**, 53 (1970).

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