

CONFORMATIONAL STUDIES—XV¹

TRANSANNULAR ELECTROSTATIC INTERACTIONS IN 4-SUBSTITUTED 1,1-DIMETHYLPYPERIDINIUM CATIONS

R. D. STOLOW, D. I. LEWIS and P. A. D'ANGELO

Department of Chemistry, Tufts University, Medford, Massachusetts 02155, U.S.A.

(Received in France 18 April 1970; Received in the UK for publication 23 July 1970)

Abstract—Conformational equilibria for 4-X-1,1-dimethylpiperidinium iodides (2-5: X = Cl, OAc, OBz, OH) were studied by measuring their C-4 proton NMR band widths in solution at 31° and 100 MHz. Under all conditions studied, and relative to the corresponding monosubstituted cyclohexane in each case, the transannular electrostatic interactions resulting from the presence of the unit positive charge on nitrogen in 2-5 stabilized the chair conformation with X axial more than that with X equatorial. The conformational equilibria showed solvent dependence not correlated by solvent dielectric constant.

The 1-t-butyl-4-hydroxy-1-methylpiperidinium iodides (21 and 22), prepared for comparison with 5, showed proton-nitrogen-14 spin-spin coupling, $J_{\text{HCCN}^{14}}$, of approx. 1.5 Hz, which split the t-butyl NMR signals into 1:1:1 triplets. The N-methyl signal of 22 was split by long range proton-proton coupling into a 1:2:1 triplet, $J_{\text{HCNCH}_3} |0.86|$ Hz, with only slight line broadening resulting from coupling to nitrogen-14, $J_{\text{HCN}^{14}} < |0.2|$ Hz.

INTRODUCTION

TRANSANNULAR electrostatic interactions in cyclohexane derivatives make an important contribution to the relative free energies of the two chair conformations, 1a and 1e, where X and Z are both polar groups. Previously, we have reported the



results for the Z groups: $\text{O}=\overset{\delta+}{\text{C}}$, $\begin{matrix} \text{F} & \delta+ \\ & \diagdown \\ & \text{C} \\ & / \\ \text{F} & \delta+ \end{matrix}$, and $\begin{matrix} \text{O} & \delta+ \\ \diagdown & \\ \text{O} & \delta+ \end{matrix} \text{C}$, among others.²⁻⁴ We found no consistent correlation between conformational energies²⁻⁴ and transannular group dipole-dipole interaction energies as calculated by use of eqn 1, the approximate method of Jeans.³

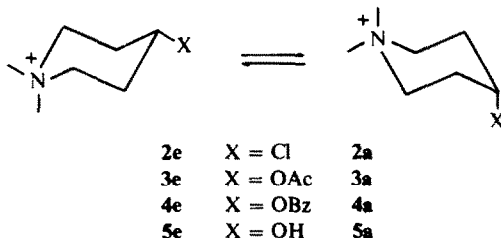
$$E = \frac{\mu_1 \mu_2}{r^3 D} (\cos \chi - 3 \cos \alpha_1 \cos \alpha_2) \quad (1)$$

In most cases, for example, for 1 with Z groups CF_2 or $\text{C}=\text{O}$ and $\text{X} = \text{Cl}^{2,4}$ or OH ,^{2,3} dipole-dipole interaction energies calculated by the approximate method of Jeans³ can be made to agree with the results if one treats the dielectric constant (D) of the medium between the dipoles as an adjustable parameter which may be given a different value for each conformation (eqn 1). However, use of such an arbitrary

procedure would be difficult to justify. Furthermore, for the ketals, 1,4-dioxaspiro[4.5]decan-8-yl³ and 8-chloro-1,4-dioxaspiro[4.5]decane,⁴ where the dipole-dipole interaction energy calculated by the approximate method of Jeans and the electrostatic interaction energy deduced from experiment are of opposite sign, no adjustment of D (defining $D \geq 1$) could give agreement. We concluded⁴ that "the approximate method of Jeans does not work."

For each of the three Z groups shown above, a partial positive charge is induced at the ring carbon transannular to group X, and in each case, it was observed that **1a** is stabilized relative to **1e** by the resulting electrostatic interactions ($X = \text{Cl}$, OH , and OBz).²⁻⁴ It appeared as if the electrostatic contribution to the conformational energies for **1** was controlled mainly by the electrostatic interaction between X and charge induced in the cyclohexane ring by Z. Charge distribution within the Z group, but external to the cyclohexane ring, appeared to be much less significant. Therefore, it seemed worthwhile to compare compounds with a unit positive charge transannular to group X (**1**, $Z = (\text{CH}_3)_2\text{N}^+$) to the compounds reviewed above,²⁻⁴ which have an induced partial positive charge transannular to group X.

In this paper, we wish to report relative conformational energies for 4-substituted 1,1-dimethylpiperidinium iodides (**2-5**) which afford electrostatic interactions involving the unit positive charge on nitrogen and the transannular polar substituent, X, at C-4. Compounds **2**, **3**, and **5** have been objects of a simultaneous study reported in an accompanying paper by M. L. Stien *et al.*⁶



RESULTS AND DISCUSSION

Conformational populations of the piperidinium iodides (**2-5**) were determined from their C-4 proton NMR band widths³⁻⁵ (W_i) recorded in Table 1, by use of the relationship:

$$W_i = N_{ia}W_{ia} + N_{ie}W_{ie} \quad (2)$$

where $N_{ia} + N_{ie} = 1$, $\Delta G^\circ = -RT \ln (N_{ia}/N_{ie})$, $i = 2-5$, W_i is the observed C-4 proton band width for compound i (measured as the frequency difference between the two outermost lines of the C-4 proton multiplet), N_{ia} is the mole fraction and W_{ia} is the specific band width of compound i in the chair conformation with the C-4 substituent *axial*, and similarly, $N_{ie} \dots$ and $W_{ie} \dots$ *equatorial*. Values of W_{ia} and W_{ie} were approximated by NMR band widths of model compounds (Table 2).

The C-4 proton of **2** in dimethyl sulfoxide- d_6 solution (Fig 1) gives a heptet apparently resulting from overlap of lines 3 and 4 and of lines 6 and 7 of a symmetrical 1:2:1:2:4:2:1:2:1 triplet of triplets. In spite of some broadening by long range coupling, the outer lines are well resolved, and their frequency separation, $W_2 = 22.2$ Hz, can be recorded with good precision. Table 1 gives C-4 proton NMR band widths

TABLE I. C-4 PROTON NMR BAND WIDTHS AND CONFORMATIONAL FREE ENERGY DIFFERENCES FOR PIPERIDINIUM IODIDES 2-5 AT 31°

Compd i	X	Models ^b for W_{6a} and W_{1a}	Solvent: DOD		Solvent: (CD ₃) ₂ SO	
			W_p , Hz	ΔG° kcal/mole ^c	W_p , Hz	ΔG° kcal/mole ^c
2	Cl	6e and 6a 7 and 8 9 and 10	19.2 ± 0.2	- 0.33	22.2 ± 0.2	+ 0.02
				- 0.28		+ 0.09
				- 0.31 ^d		+ 0.04 ^e
3	OAc	11e and 11a 12 and 13	17.4 ± 0.2	- 0.46	20.4 ± 0.2	- 0.08
				- 0.45		- 0.09
4	OBz	14 and 15 16 and 15	17.1 ± 0.6	- 0.5	18.5 ± 0.4	- 0.31
				- 0.6		- 0.37
5	OH	17 and 18 19 and 20 21 and 22	22.6 ± 0.2 ^f	+ 0.23	21.2 ± 0.4 ^f	+ 0.06
				+ 0.16 ^d		+ 0.01 ^e
				- 0.01		

^a Under these conditions, conformational interconversion is rapid on the NMR time scale for 2-5

^b See Table II

^c ± 0.1 kcal/mole, not including error inherent in use of models

^d Based on values from Table 2 for solvent B

^e Based on values from Table 2 for solvent A

^f Rapid exchange of hydroxyl hydrogen was observed

for 2-5 in deuterium oxide and dimethyl sulfoxide-d₆ solutions. Table 3 presents band widths for 2 in five solvents. The C-4 proton multiplet pictured in Fig 1 is a typical example of those for which band widths have been recorded in Tables 1 and 3. Clearly, a change in solvent can result in a substantial change in band width, which we have interpreted in terms of a significant solvent dependence of the conformational free energy differences (ΔG°), for 2-5. As discussed further below, the solvent dependence does not correlate with solvent dielectric constant.

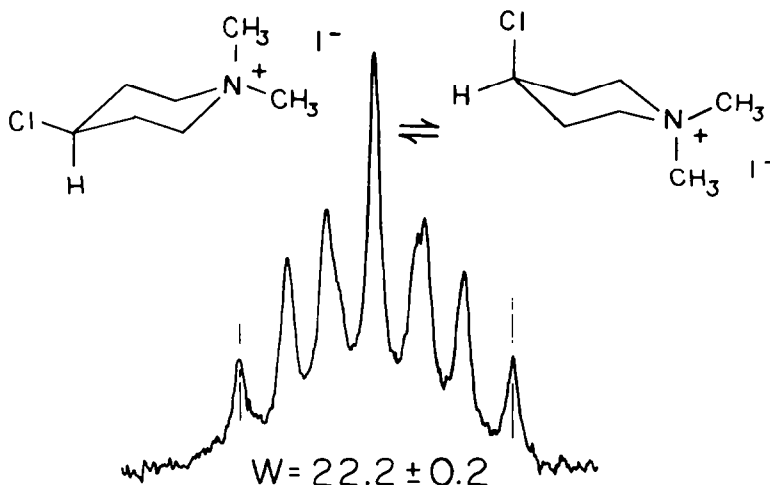
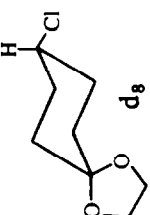
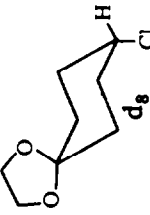
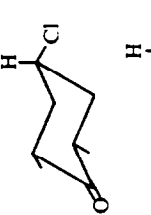
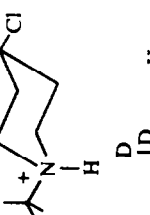
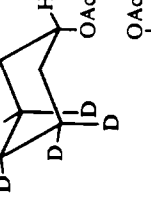
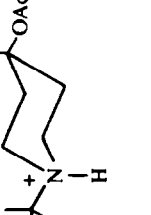
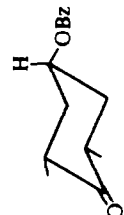

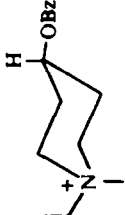
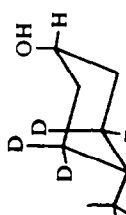
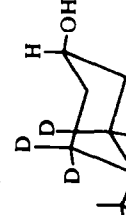


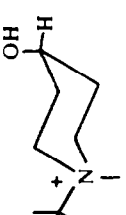
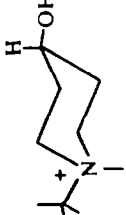


FIG 1. The C-4 proton NMR spectrum of 4-chloro-1,1-dimethylpiperidinium iodide (2) in dimethyl sulfoxide-d₆ solution at 31°

TABLE 2. NMR BAND WIDTHS OF MODEL COMPOUNDS USED TO APPROXIMATE W_a AND W_m OF 2-5

Compound	W_a	Compound	W_m	Solvent ^a	T, °	Ref
	32.45 ±0.05		11.6 ±0.1	(CD ₃) ₂ CO	-74	4
7	31.5 ±0.1		11.4 ±0.2	CCl ₄	31	4
9	32.0 31.8		11.8 11.6	A B	31 31	6 6
11e	31.34 ±0.4		10.84 ±0.4	CS ₂	-110	7
12	31.8		10.6	A	31	6

14		31.1 ±0.1	15		10.9 ±0.1	(CD ₃) ₂ SO	31	3
16		32.6 ±0.2	18		10.7 ±0.4	(CD ₃) ₂ SO	31	b
17		30.8 ±0.4	20		10.0 10.6	DCCl ₃	28	7
19		32.2 31.8	22		11.9 ±1	A B	31 31	6 6
21		33.4 ±1				D ₂ O	31	b

^a Solvent A: 80% trifluoroacetic acid plus 20% DCCl₃ (volume)

Solvent B: 90% HCl plus 10% D₂O

^b This work

TABLE 3. SOLVENT DEPENDENCE OF THE C-4 PROTON NMR BAND WIDTH OF 4-CHLORO-1,1-DIMETHYL-PIPERIDINIUM IODIDE (2), AT 31°

Solvent	W_2 , Hz	% axial ^a	ΔG_2° , kcal/mole ^a
(D ₃ C) ₂ SO	22.2 ± 0.2 ^b	49.0 ± 1.8	+ 0.02 ± 0.04
D ₃ CCN	20.6 ± 0.3	56.7 ± 2.1	- 0.16 ± 0.05
D ₃ COD	20.6 ± 0.2	56.7 ± 1.6	- 0.16 ± 0.04
DOD	19.2 ± 0.2	63.4 ± 1.6	- 0.33 ± 0.04
A ^c	17 ^d	74	- 0.64 ^d

^a Stated limits of error do not include the contribution to the error inherent in the use of model compounds

^b See Fig 1

^c Solvent A: 80% trifluoroacetic acid plus 20% DCCl₃ (volume)

^d Values reported by J. Reisse and M. L. Stien.⁶ This extreme result, when repeated in our laboratory for solvent A, was confirmed: W_2 , 16.3 ± 0.2 Hz, ΔG_2° , - 0.75 ± 0.08 kcal/mole

TABLE 4. CONCENTRATION DEPENDENCE OF THE C-4 PROTON NMR SIGNAL OF 2 IN D₂O AT 31°

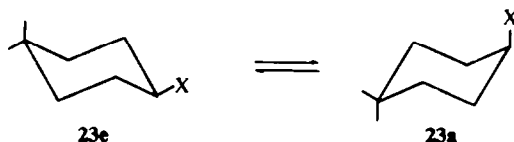
Conc M	Band Width W_2 , Hz	Chemical Shift δ , ppm
0.09	19.3 ± 0.5	4.966
0.14	19.2 ± 0.3	4.979
0.36	19.2 ± 0.2	5.008
0.81	19.2 ± 0.2	5.057

Table 4 shows that for 2 in deuterium oxide at 31°, the C-4 proton NMR band width (and presumably the conformational equilibrium) remains essentially constant as the concentration of 2 is increased up to ninefold. However, under these conditions, the chemical shift of the C-4 proton increases significantly with concentration (Table 4). Even for model compounds (Table 2), chemical shifts were sensitive to changes in temperature, concentration, solvent, and remote substituents to such an extent that conformational populations could not be deduced from chemical shift data for 2-5. The advantage of estimating conformational populations from C-4 proton band widths, rather than chemical shifts, is the relative lack of sensitivity of band widths of model compounds (Table 2) to factors other than the configuration of the C-4 proton. Furthermore, identity of the X group (for X = Cl, OAc, OBz, or OH) is but a minor factor influencing C-4 proton band width; the values of W_e are 30.8-33.4 Hz, and W_n , 10.0-11.9 Hz for the model compounds cited having X = OH (Table 2). All other models cited in Table 2 (X = Cl, OAc, and OBz) give values of W_e and W_n within the same range as those with X = OH.

Each conformational free energy difference (ΔG°) given in Table 1 is based upon a pair of model compounds from Table 2 having the same X group as compound i. For each compound in each solvent, the two or three ΔG° values given (Table 1) are in good agreement (± 0.1 kcal/mole or better), except for 5 in D₂O. The model compounds most closely related in structure to 5, the 1-t-butyl-4-hydroxy-1-methylpiperidinium

iodides (**21** and **22**), give the largest W_e and W_a values in Table 2, 33.4 ± 1 and 11.9 ± 1 Hz, respectively. When these values are used to approximate W_{e^*} and W_{a^*} , respectively (Table 1, last entry), the result, $\Delta G^\circ = -0.01$ kcal/mole, is significantly more negative than the values based upon model compounds **17–20**. This more negative value may be closest to the truth, since **5**, **21**, and **22** were all studied in the same solvent and at the same temperature (D_2O at 31°) and **21** and **22** are the best available model compounds for **5e** and **5a**. For *trans*-4-benzoyloxy-1-*t*-butyl-1-methylpiperidinium iodide (**16**) in dimethyl sulfoxide- d_6 , $W_e = 32.6 \pm 0.2$ Hz, a value 1.5 Hz larger than W_e for **14** in the same solvent. Since only **16**, **21**, and **22** are piperidinium salts with axial N-methyl groups, it is conceivable that those model compounds in Table 2 lacking this structural feature may underestimate W_{e^*} and W_{a^*} slightly for **2–5**. Therefore, any error introduced by using model compounds other than the closely related piperidinium iodides, **16**, **21**, and **22** (Table 2) to approximate W_{e^*} and W_{a^*} for **2–5** most likely results in slight overestimation of ΔG° (i.e. ΔG° too positive, indicating slight underestimation of the population of conformer **a** in which the X group is axial).

Under all conditions studied for **2–5** (Table 1), conformer **a** was stabilized relative to **e** by the electrostatic interactions present as compared with the corresponding monosubstituted cyclohexanes⁹ or the more closely related 4,4-dimethylcyclohexanes (**23**)¹⁰ which have nonpolar Z groups (1,Z = CH_2 or CMe_2) transannular to group X. For example, compare the conformational free energy differences of 4-chloro-1,1-



dimethylcyclohexane (**23**, X = Cl), $\Delta G_{23}^\circ = 0.43$ kcal/mole in decalin solution at 25° ,¹⁰ and 4-chloro-1,1-dimethylpiperidinium iodide (**2**), $\Delta G_2^\circ = 0$ to -0.7 kcal/mole (Table 3). The difference, $\Delta G_2^\circ - \Delta G_{23}^\circ = -0.4$ to -1.2 kcal/mole, depending upon the solvent, reflects the influence of the electrostatic interaction energy favoring **2a** over **2e**, and may be compared with a theoretical value, $\Delta E = -3.5$ kcal/mole, the Coulombic interaction energy difference between the nitrogen–chlorine interactions in **2a** and **2e** which would result if the interactions occurred between isolated charges in empty space.

Assuming that the distances between C-4 and nitrogen are the same in **2a** and **2e**, then from the exact equation for interaction between an ion and a permanent dipole,¹¹ one can derive the equation:

$$\Delta E = E_a - E_e = e_N e_{Cl} (1/r_e - 1/r_a) \quad (3)$$

where r_e and r_a are nitrogen–chlorine distances in **2e** and **2a**, e_N is the unit positive charge on nitrogen (4.803×10^{-10} esu), and e_{Cl} is the absolute value of the partial negative charge on chlorine evaluated as $e_{Cl} = \mu/d$, where μ is taken as the dipole moment of chlorocyclohexane, 2.2×10^{-18} esu·cm,¹² and the C–Cl bond length,¹³ d , is taken as 1.77×10^{-8} cm. Then $e_{Cl} = 1.24 \times 10^{-10}$ esu. Approximating $r_e = 4.43 \times 10^{-8}$ cm and $r_a = 3.76 \times 10^{-8}$ cm by measurement of Dreiding molecular models of **2e** and **2a**, the electrostatic interaction energy difference for **2e** \rightleftharpoons **2a** may be calculated: (eqn 3) $\Delta E = -3.5$ kcal/mole. Thus, for an isolated unity positive

charge (e_N) and an isolated partial negative charge (e_{Cl}) interacting through empty space, the electrostatic interaction strongly favors the axial conformer (**2a**) simply because $r_a < r_e$. However, the substantial energy difference (ΔE) calculated for the isolated charges is reduced considerably in the presence of the intervening bonded atoms, solvent molecules, and iodide anions.

The relative stabilization of **2a**, **3a**, and **4a** is greater in deuterium oxide than in dimethyl sulfoxide- d_6 , but since deuterium oxide has the greater dielectric constant, the reverse might have been expected. Clearly, dielectric constant of the solvent itself is not the factor controlling solvent dependence of relative conformational energies for **2-4**. It is not enough to consider only some hypothetical bulk property, such as an effective dielectric constant of the intervening bonded atoms, associated ions, and solvent molecules which occupy the space between the charges. One cannot justify use of an effective dielectric constant as an adjustable parameter calculated merely to fit the data. Specific solute-solvent and solute-solute interactions (including ion pairing and entropy differences) require elucidation before the solvent dependent conformational energies of the piperidinium cations of **2-5** may be understood. We conclude that electrostatic interactions within the cation are moderated by the medium, but that moderation is not explainable as resulting from a bulk property of the medium (such as dielectric constant); the time-averaged specific interactions between the cation and associated species in solution exert a substantial influence upon conformational energies.

In this paper, we have focused attention upon the unit positive charge on nitrogen transannular to a substituent, X, in the piperidinium iodides (**2-5**). We observe qualitatively that the unit positive charge influences conformational energies in the same manner as does a partial positive charge at the same position induced by dipolar substituents in related cyclohexane derivatives (**1**).²⁻⁴ The analogy is apparently a useful one. However, the problem of evaluating electrostatic interaction energies is far more complex than merely solving an equation like eqn 3, above. The transannular charge on the ring (**1-5**) induces a pattern of charge distribution throughout the molecule. One would like a reliable method for calculation of the expected induced charge distribution and for evaluation of the net interaction energy among all charges present in each conformation in order to estimate the electrostatic contribution to conformational energies. Although it may be possible to represent the problem by a network of three or more effective point charges, most simply, centered upon the nuclei, and sum the pairwise Coulombic interactions, any procedure which treats either the magnitude or position of an effective point charge as an adjustable parameter would be suspect. A solution of the problem for simple isolated molecules, neglecting specific interactions with neighboring species (i.e., the medium), may be feasible by quantum mechanical calculations.

PROTON-NITROGEN-14 SPIN-SPIN COUPLINGS

In determining the composition of product mixtures of *trans*- and *cis*-1-*t*-butyl-4-hydroxy-1-methylpiperidinium iodide (**21** and **22**) it was desirable to see in the NMR spectrum of the mixture a single, sharp *t*-butyl peak for each isomer. To achieve this result, nitrogen-14 was irradiated in order to remove from the spectrum the splittings caused by proton-nitrogen-14 spin-spin couplings. Changes observed in the decoupled spectra are discussed below.

A 1:1 mixture of *trans*- and *cis*-1-*t*-butyl-4-hydroxy-1-methylpiperidinium iodide (**21** and **22**) in deuterium oxide solution gave a 100 MHz NMR spectrum with four overlapping peaks at 198.1, 199.6, 201.2, and approx. 202.3 Hz downfield from external TMS, with intensities 1:2:2:1 (Fig 2). The total integrated area of these peaks relative to the other peaks in the spectrum supported their assignment to the *t*-butyl groups of **21** and **22**. The observed pattern (Fig 2) resulted from overlapping of two 1:1:1 triplets, one triplet for each *t*-butyl group, caused by H—C—C—N¹⁴ coupling.¹⁴⁻¹⁷ Upon irradiation of the nitrogen-14 nuclei at 7.224244 MHz, each 1:1:1 triplet collapsed to give a singlet, one at 199.8 Hz, the other at 200.9 Hz (widths at half-height < 0.6 Hz, see Fig 3).

A similar 3:1 mixture of **21** and **22** showed four overlapping peaks at 198.7, 200.3, 201.6 and approx. 202.7 Hz with intensities 3:4:4:1. Irradiation of nitrogen-14 gave a *t*-butyl singlet at 200.5 Hz, and a second *t*-butyl singlet, about one-third as intense, at 201.7 Hz. The latter *t*-butyl peak may therefore be assigned to the minor component, **22**.

The values of the coupling constants, $J_{\text{HCCN}^{14}}$, appear to be 1.6 ± 0.2 Hz for **21** and 1.4 ± 0.3 Hz for **22**. These values for H—C—C—N¹⁴ couplings are similar to values reported for *t*-butyltrimethylammonium iodide¹⁴ in the same solvent (D₂O), $J_{\text{HCCN}^{14}}$, 1.74 ± 0.04 Hz, and for tetraethylammonium salts,¹⁴⁻¹⁷ $J_{\text{HCCN}^{14}}$, 1.8 Hz. In contrast, values reported^{15, 17} for these and related quaternary ammonium salts for H—C—N¹⁴ couplings often are very small, $J_{\text{HCN}^{14}}$, approx. $|0.2|$ Hz.

In agreement with these reports, very small values of $J_{\text{HCN}^{14}}$ were detected for the N-methyl groups of **21** and **22**, (1:1 mixture, D₂O solution, 100 MHz) as shown by the change in the NMR spectrum of the N-methyl groups upon irradiation of the nitrogen-14 nuclei at 7.224234 MHz (Fig 4). With heteronuclear decoupling of nitrogen-14, the N-methyl peak of **22** appeared as a 1:2:1 triplet with lines at 346.26, 347.12, and 347.97 ± 0.05 Hz (the triplet most likely results from long range proton-proton coupling between the protons of the axial N-methyl group and the axial ring protons at C-2 and C-6, with $J_{\text{HCNCH}} = |0.86| \pm 0.1$ Hz); the N-methyl peak of **21** at 350.8 Hz, showed no fine structure, but the band width at half height, 1.4 Hz, showed broadening most likely resulting from long range H—C—N—C—H coupling ($J_{\text{HCNCH}} < 0.7$ Hz). Without heteronuclear decoupling of nitrogen-14 (Fig 5), the band width at half height increased by approx. 0.35 Hz for both **21** and **22**: $J_{\text{HCN}^{14}} < |0.2|$ Hz. The line broadening observed in Fig 5 as compared to Fig 4 would probably be accounted for by $J_{\text{HCN}^{14}} = |0.15| \pm 0.05$ Hz.

4-Chloro-1,1-dimethylpiperidinium iodide (**2**), in dimethyl sulfoxide-d₆ solution, gave two N-methyl peaks which showed no resolved fine structure, but which were broadened slightly by long range H—C—N—C—H coupling (band widths at half height with nitrogen-14 irradiated, 1.4 and 1.5 Hz), and were broadened further by very small H—C—N¹⁴ coupling (band widths at half-height without irradiation of nitrogen-14, 1.6 and 1.8 Hz).

Long range H—C—C—C—N¹⁴ coupling involving the proton at C-4 of **21** must also be very small. The line widths within the C-4 proton multiplet appeared to decrease slightly upon irradiation of nitrogen-14, but most likely, $J_{\text{HCCCN}^{14}} < |0.2|$ Hz. It is important to note that the C-4 proton band width is not significantly influenced by long range H—C—C—C—N¹⁴ coupling for **21**.

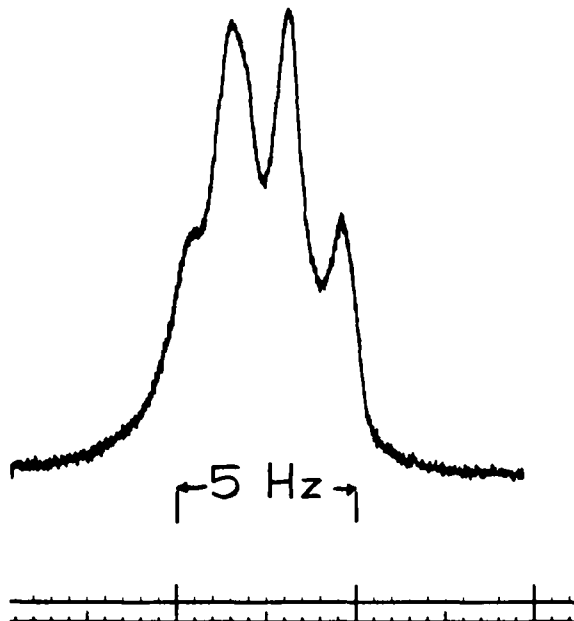


FIG 2. The t-butyl proton region of the NMR spectrum of a 1:1 mixture of *trans*- and *cis*-1-t-butyl-4-hydroxy-1-methylpiperidinium iodide (**21** and **22**) in deuterium oxide solution at 31°, showing splitting by proton-nitrogen-14 coupling

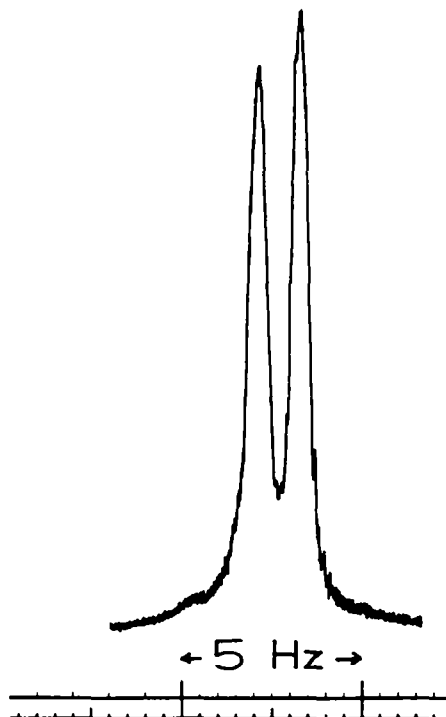


FIG 3. Same t-butyl proton NMR spectrum as Fig 2, but with nitrogen-14 nuclei decoupled, showing a singlet for each stereoisomer.

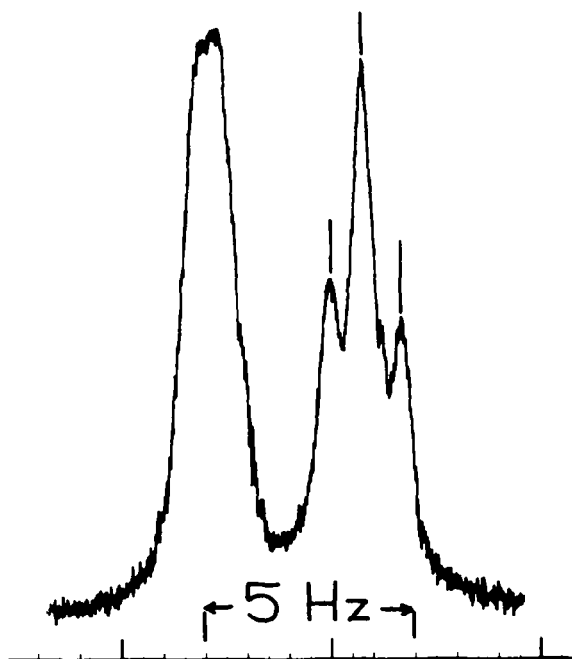


FIG 4. The N-methyl proton region of the NMR spectrum of a 1:1 mixture of 21 and 22 in deuterium oxide solution at 31°, with nitrogen-14 nuclei decoupled, showing splitting by long range proton-proton coupling for 22.

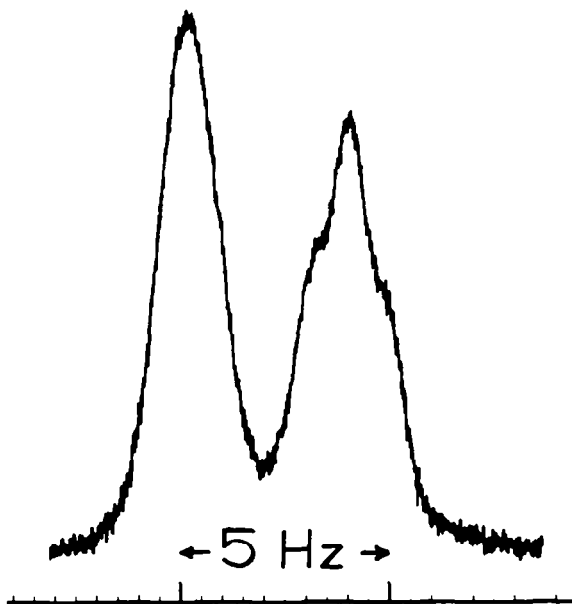
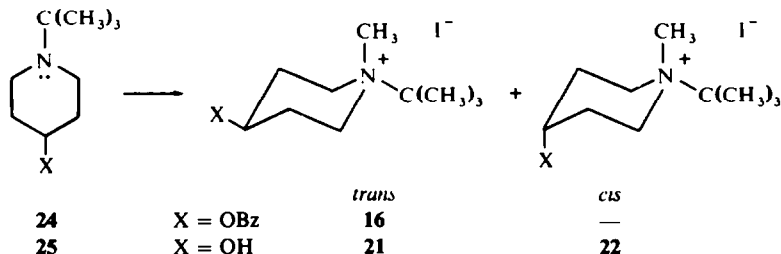


FIG 5. Same N-methyl proton NMR spectrum as Fig 4, but without any decoupling. Comparison with Fig 4 shows that H—C—N¹⁴ coupling here must be very small

SYNTHESIS

The piperidinium iodides (**2-5**, **16**, **21**, and **22**) were prepared by the reaction of the



corresponding 1-alkylpiperidine with iodomethane. From the mixture of *cis*- and *trans*-isomers prepared from **24**, the *trans*-isomer (**16**) was isolated by recrystallization. An attempt to separate the *trans*-isomer (**21**) from the *cis*-isomer (**22**) by recrystallization gave a sample enriched in **21**. The two component mixtures of stereoisomers (**21** and **22**) were analyzed by NMR spectrometry of solutions in deuterium oxide.

EXPERIMENTAL

M.p.s. were determined in Pyrex capillaries with a Büchi apparatus and are corrected. IR spectra of samples in KBr pellets were recorded on a Perkin-Elmer 237B Spectrophotometer. NMR spectra of 0.1–0.2 M sol at 31° were obtained by use of a Varian HA-100 Spectrometer. NMR data are given in the order: solvent, chemical shift (δ) in ppm downfield from external TMS (multiplicity, where s = singlet, d = doublet, t = triplet, m = multiplet, integration, assignment). For irradiation of nitrogen-14 an NMR Specialties HD-60B Heteronuclear Decoupler was used. Microanalyses were performed by M—H—W Laboratories, Garden City, Michigan.

4-Chloro-1,1-dimethylpiperidinium iodide (2). 4-Chloro-1-methylpiperidine hydrochloride (40 g, Eastman) was dissolved in H₂O (10 ml), and 6N KOH (4.3 ml) was added at 0°. The liberated amine was extracted with Et₂O (20 ml), and the ether layer was dried over Na₂SO₄. MeI (6.8 g), dissolved in Et₂O (20 ml), was slowly added to the filtered ether solution. The solution, allowed to stand overnight at approx. 5°, yielded a white solid (3.9 g), which after recrystallization from MeOH, gave m.p. 221.5–223.5° (with decomposition).

IR (C—Cl, cm⁻¹): 700 (med), 735 (strong); NMR: (CD₃)₂SO, 4.86 (m, 1, Cl—C—H), 3.92 (t, 4, N—CH₂—C), 3.60 (s, C, CH₃), 3.55 (s, 3, CH₃), 3.1–2.3 (m, 4, C—CH₂—C)

Analysis. Found: C, 30.35; H, 5.70; N, 4.98. Calc for C₇H₁₃ClIN: C, 30.51; H, 5.49; Cl, 12.87; I, 46.05; N, 5.08%.

4-Acetoxy-1,1-dimethylpiperidinium iodide (3). 4-Hydroxy-1-methylpiperidine (5.0 g, Aldrich) was dissolved in Et₂O (50 ml); AcCl (6.8 g) was added dropwise with stirring (15 min) at 0°. After stirring at approx. 23° (30 min), EtOH (10 ml) and 10% NaOH (10 ml) were added, and the reaction mixture extracted with Et₂O. The extract was dried over MgSO₄. Concentration gave 4-acetoxy-1-methylpiperidine as a pale yellow oil (3.73 g). To this oil dissolved in EtOH (12 ml) was added CH₃I (2.33 g). The soln was heated under reflux (40 min); Et₂O freshly distilled from SnCl₂ (100 ml) was added to the cooled reaction mixture. The resulting white solid (2.16 g), after recrystallization from EtOH, gave m.p. 164–165°; IR 1740 cm⁻¹ (acetate C=O); NMR: (CD₃)₂SO, 5.28 (m, 1, O—C—H), 4.0–3.6 (m, N—CH₂—C), 3.59 (s, 3, CH₃), 3.54 (s, 3, CH₃), 2.47 (s, OCCH₃), ~ 2.7–2.1 (m, C—CH₂—C).

Analysis. Found: C, 36.17; H, 6.25; I, 42.46; N, 4.59. Calc for C₉H₁₈INO₂: C, 36.13; H, 6.06; I, 42.42; N, 4.68; O, 10.70%.

4-Benzoyloxy-1,1-dimethylpiperidinium iodide (4). 4-Benzoyloxy-1-methylpiperidine hydrochloride (m.p. 220–221° with decomposition) was prepared by the method of Bolyard and McElvain.¹⁸ N NaOH (30 ml) was added to the hydrochloride salt (4.3 g), and the liberated amine was extracted into Et₂O. The ether soln

was dried over MgSO_4 , followed by concentration to yield the amine as a yellow oil. This compound was dissolved in EtOH (20 ml), and CH_3I (3.2 g) was added dropwise with stirring. The mixture was heated at reflux (40 min); Et_2O freshly distilled from SnCl_2 (100 ml) was added to the cooled reaction mixture. The resulting white solid (5.5 g) after recrystallization from EtOH gave m.p. 171.5–172.5°; IR 1740 cm^{-1} (benzoate $\text{C}=\text{O}$), 1600, 1580 cm^{-1} ; NMR: $(\text{CD}_3)_2\text{SO}$, 8.6–7.8 (m, 5, C_6H_5), 5.58 (m, 1, $\text{O}-\text{C}-\text{H}$), 4.2–3.8 (m, $\text{N}-\text{CH}_2-\text{C}$), 3.69 (s, 3, CH_3), 3.62 (s, 3, CH_3), 2.9–2.4 (m, 4, $\text{C}-\text{CH}_2-\text{C}$).

Analysis, Found: C, 46.56; H, 5.68; I, 35.05; N, 3.76. Calc for $\text{C}_{14}\text{H}_{20}\text{INO}_2$: C, 46.55; H, 5.58; I, 35.13; N, 3.88; O, 8.86%.

4-Hydroxy-1,1-dimethylpiperidinium iodide (5). By the method of Craig and Tarbell,¹⁹ 4-hydroxy-1-methylpiperidine (Aldrich) was converted to **5**, m.p. 334.5–335.5° (with decomposition, uncorrected, Mel-Temp apparatus) (lit.¹⁹ m.p. 309–311° with decomposition); IR 3340 cm^{-1} ($\text{O}-\text{H}$); NMR: $(\text{CD}_3)_2\text{SO}$ + trace $\text{D}_2\text{O}/\text{DCI}$, 4.25 (m, $\text{O}-\text{C}-\text{H}$), 4.05 (s, 1, OH), 4.0–3.7 (m, 4, $\text{N}-\text{CH}_2-\text{C}$), 3.54 (s, 6, CH_3)*, 2.64–1.92 (m, 4, $\text{C}-\text{CH}_2-\text{C}$).

1-t-Butyl-4-hydroxypiperidine (25). 1-t-Butyl-4-piperidone (3.03 g, b.p. 73–74.5°/2 mm) prepared by the method of Robinson and Thomas²⁰ (lit.²⁰ b.p. 92–94°/9 mm; lit.²¹ b.p. 93–94°/11 mm) was dissolved in MeOH (15 ml) and NaBH_4 (0.63 g) was added. The sol was stirred at approx. 23° ($\frac{1}{2}$ hr); then excess borohydride was decomposed with 10% HCl soln (50 ml). The soln was made basic with NaHCO_3 , and MeOH was removed under vacuum. The aqueous soln was saturated with NaCl and extracted with Et_2O . The combined ether layers were dried over MgSO_4 , followed by concentration to give 2.1 g of 1-t-butyl-4-hydroxypiperidine (**25**), b.p. 80–82°/0.1 mm, mp 41–42.5° without recrystallization [lit.,²¹ b.p. 109–110°/11 mm, m.p. 60–61°].

trans and *cis*-1-t-Butyl-4-hydroxy-1-methylpiperidinium iodides **21** and **22**.

1-t-Butyl-4-hydroxypiperidine **25** (0.51 g), and CH_3I (1.2 g) were dissolved in benzene (70 ml) and heated under reflux (48 h) to give a mixture of *cis* and *trans*-1-t-butyl-4-hydroxy-1-methylpiperidinium iodide (0.85 g), m.p. 191–192° (with decomposition) after recrystallization from EtOH; IR 3380 cm^{-1} ($\text{O}-\text{H}$); NMR: $(\text{CD}_3)_2\text{SO}$ + trace $\text{DCI}/\text{D}_2\text{O}$, 3.8–4.4 ($\text{O}-\text{C}-\text{H}$ both *cis* and *trans*), 3.98 (s, OH), 4.1–3.4 (m, $\text{N}-\text{CH}_2-\text{C}$), 3.34 (s, 3, CH_3), 2.7–2.1 (m, 4, $\text{C}-\text{CH}_2-\text{C}$), 1.83 (single peak,²² width at half height, 4.0 Hz, 9, $\text{C}(\text{CH}_3)_3$), recorded at sweep width, 10 Hz/cm. Note that **21** and **22** gave coincident methyl and coincident t-butyl peaks under these conditions. NMR: D_2O , with irradiation of nitrogen-14, 4.63 (quintet, equatorial C-4 proton of **22**), 4.40 (heptet, axial C-4 proton of **21**), 4.2–3.5 (m, $\text{N}-\text{CH}_2-\text{C}$), 3.51 (s, CH_3 of **21**), 3.47 (t, CH_3 of **22**), 2.9–2.0 (m, $\text{C}-\text{CH}_2-\text{C}$), 2.01 (s, $\text{C}(\text{CH}_3)_3$ of **22**), 2.00 (s, $\text{C}(\text{CH}_3)_3$ of **21**), see Fig 2-5.

Analysis, Found: C, 39.73; 40.13; H, 7.65, 7.53; N, 4.68. Calc for $\text{C}_{10}\text{H}_{22}\text{INO}$: C, 40.14; H, 7.41; I, 42.42; N, 4.68; O, 5.35%.

trans-4-Benzoyloxy-1-t-butyl-1-methylpiperidinium iodide (16). A mixture of 1-t-butyl-4-hydroxypiperidine (**25**, 0.52 g), benzoyl chloride (0.52 g), and benzene (5 ml) was heated under reflux (48 h). Then 10% HCl (0.3 ml) and EtOH (3 ml) were added to the reaction mixture, followed by 10% NaOH (10 ml). The mixture was then extracted with Et_2O . The combined ether layers were washed with Et_2O and dried over MgSO_4 , followed by concentration to give 4-benzoyloxy-1-t-butylpiperidine (**24**, 1.1 g), a pale yellow oil. To this oil dissolved in benzene (50 ml) was added CH_3I (0.7 g). The mixture was heated under reflux (48 h) to yield a crude mixture of *cis*- and *trans*-4-benzoyloxy-1-t-butyl-1-methylpiperidinium iodide (0.49 g). Recrystallization from $\text{Et}_2\text{O}-\text{EtOH}$ gave the *trans*-isomer (**16**) (benzoyloxy group equatorial, C-4 proton band width 32.5 Hz), m.p. 196.5–197.5° (with decomposition); IR 1720 cm^{-1} (benzoate $\text{C}=\text{O}$), 1600, 1580 cm^{-1} ; NMR: $(\text{CD}_3)_2\text{SO}$, 8.5–7.8 (m, 5, C_6H_5), 5.57 (m, 1, $\text{O}-\text{C}-\text{H}$), 4.2–3.0 (m, $\text{N}-\text{CH}_2-\text{C}$), 3.41 (s, 3, CH_3), 2.8–2.4 (m, 4, $\text{C}-\text{CH}_2-\text{C}$), 1.80 (single peak,²² width at half height, approx. 3.5 Hz, 9, $(\text{CH}_3)_3\text{C}$), recorded at sweep width, 20 Hz/cm.

Analysis, Found: C, 50.56; H, 6.68; I, 31.30; N, 3.60. Calc for $\text{C}_{17}\text{H}_{26}\text{INO}_2$: C, 50.63; H, 6.50; I, 31.47; N, 3.47; O, 7.93%.

Acknowledgements—We wish to thank the Research Corporation and the National Science Foundation for support of this work. The 100 MHz NMR Spectrometer and Heteronuclear Decoupler were purchased with matching funds from NSF Grant GP 8171. We are most grateful to Dr. J. Reisse for informing us of his results in advance of publication.⁶

* Accidental coincidence of the two methyl group chemical shifts, observed under these conditions, is not observed in D_2O solution.

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