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Conformational Analysis. 39.[1] ^{13}C NMR Spectra of Saturated Heterocycles. 9.[2] Piperidine and *N*-Methylpiperidine

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Abstract: The ^{13}C NMR spectra of 16 *C*-methyl-substituted piperidines and 19 *N,C*-dimethyl-substituted piperidines as well as *N*-*tert*-butyl-3- and -4-methylpiperidine have been recorded and (separate) methyl substitution parameters for the piperidine and *N*-methylpiperidine chemical shifts have been computed. Shifts calculated using these parameters and experimental shifts are in excellent agreement. Also recorded were the spectra of 25 hydrochlorides of many of the above *N*-alkylpiperidines. Conformational analysis of the C-methylated and dimethylated piperidines and their *N*-methyl derivatives was undertaken through measurement of their spectra at −80 to −100 °C, and the following free-energy differences between equatorial and axial *C*-methyl groups were deduced: N-H compounds, 2-Me, 2.5 kcal/mol; 3-Me, 1.6 kcal/mol; 4-Me, 1.9 kcal/mol; N-Me compounds, 2-Me, 1.7 kcal/mol; 3-Me, 1.6 kcal/mol; 4-Me, 1.8 kcal/mol. The variously substituted *N*-methylpiperidinium hydrochlorides were readily equilibrated in D_2O at a pH of about 5; corresponding $\Delta G°$ values are for 2-Me, 1.4 kcal/mol; 3-Me, 2.2 ± 0.4 kcal/mol; 4-Me, 1.6 kcal/mol. The $\Delta G°$ value for the *N*-methyl group in *N*-methylpiperidinium chloride, 2.1 kcal/mol, is *less* than the corresponding value previously found in the free base. Free-energy values for vicinal interactions in *N*,2-dimethylpiperidinium salts: N-Me_e/2-Me_a, 0.6–0.8 kcal/mol; N-Me_e/2-Me_e, 1.3–1.5 kcal/mol; N-Me_a/2-Me_e, 0.6–0.8 kcal/mol. The e/a and a/e interactions between cis-placed 2,3-dimethyl groups differ by less than 0.1 kcal/mol and the corresponding interactions between *cis*-3,4-dimethyl groups differ by about 0.2 kcal/mol.

Among six-membered saturated heterocycles, the piperidine nucleus is one of the most important ones because of its occurrence in many alkaloids as well as in artifacts of pharmacological importance. Yet literature data concerning the conformation of piperidine and *N*-alkylpiperidines are fragmentary. The stereochemistry of these ring systems has been recently reviewed.[3] The piperidine ring is in a chair conformation with a barrier to reversal of 10.4 kcal/mol[4] and a nitrogen inversion barrier of 6.1 kcal/mol.[5] After some initial confusion[6] it was recognized that the *N*-methyl group in *N*-methylpiperidine prefers the equatorial position, but the extent of the preference was long in doubt.[7] It now seems clear that this preference is quite extreme,[8,9] amounting to 3.15 ± 0.1 kcal/mol in the gas phase, 2.99 ± 0.1 kcal/mol in dodecane, and 2.41 ± 0.1 kcal/mol in chloroform;[10] our own earlier value of $1.35 < \Delta G° < 1.77$ kcal/mol was evidently too low because of difficulties with the adequacy of the model compounds used in the ^{13}C NMR study.[7,11] The question of the N-H equilibrium in piperidine itself has been even more controversial with some investigators holding that the equatorial position was preferred[12] whereas others favored the axial.[13] A recent careful low-temperature NMR study[5] gives a $-\Delta G°$ value of 0.36 kcal/mol for the N-H (a ⇌ e) equilibrium with the equatorial position most likely preferred and an even more recent infrared study of the 8-*tert*-butyl-*trans*-decahydroquinolines[1] now leaves no doubt that equatorial N-H is favored.

Conformational equilibria in *C*-methylpiperidines and N,C-methylated piperidines have been reported only in our own preliminary account[14] and in a brief note by Booth,[15] although there has been extensive work on methyl-substituted *cis*-decahydroquinolines.[16,17] We have also reported, in preliminary form, data on equilibria in *C*-methylpiperidinium salts[18] and their *N*-methyl homologues.

The principal tool used in the present work to elucidate the conformation of *C*-methyl substituted piperidines has been ^{13}C NMR spectroscopy. Earlier work on ^{13}C NMR in piperidines has been carried out by Jones,[19] Feltkamp,[20] Booth,[21] and Duch[22] and an extensive review of ^{13}C NMR spectra of saturated heterocycles (including piperidines) has just become available.[23]

Results

^{13}C NMR Spectra. The ^{13}C chemical shifts of 16 piperidines are presented in Table I and those of 19 *N*-methylpiperidines in Table II. Assignments were made by off-resonance decoupling, by comparison of chemical shifts with literature values, and from signal intensities and were generally straightforward. They were confirmed by the good agreement of experimental and calculated spectra (see below). The NH compounds have previously been studied;[19-22] our data are in only modestly good agreement with those earlier reported, with deviations ranging from 0.2 to 1.0 ppm. Such deviations are not uncommon when comparison is made with data obtained prior to 1973 and may have their origin partly in solvent and referencing differences;[24] we note that, although our shifts are almost uniformly upfield from those in the literature, this is not due to any kind of constant offset, the difference for different signals in one and the same compound ranging from 0.2 to 1.0 ppm.[20b] Only a limited amount of published data concerning *N*-methylpiperidines[19,21,22,25,26] is available; our agreement with them is no better than for the NH compounds.

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Table I. Experimental and Calculated[a] Shifts for C-Methylated Piperidines[b]

compd	C substituent	C(2)	C(3)	C(4)	C(5)	C(6)	C-Me[c]	C-Me[d]
1	none	47.6_0	27.3_6	25.3_1	27.3_6	47.6_0		
		(47.6_1)	(27.3_7)	(25.3_0)	(27.3_7)	(47.6_1)		
2	2-Me	52.4_2	34.9_2	25.0_5	26.3_9	47.3_1	23.2_0	
		(52.5_3)	(35.0_3)	(25.0_8)	(26.4_7)	47.3_2)		
3	3-Me	54.9_0	32.4_4	33.8_2	26.9_8	46.9_0	19.7_7	
		(54.8_0)	(32.3_5)	(33.8_3)	26.8_0	(46.9_2)		
4	4-Me	46.9_2	35.7_7	31.4_3	35.7_7	46.9_0	22.6_4	
		(46.8_6)	(35.8_2)	(31.4_1)	(35.8_2)	(46.8_6)		
5	*cis*-2,3-di-Me[e]	54.2_3	33.2_3	31.5_4	22.3_1	46.1_0	18.7_4	12.8_7
6	*trans*-2,3-di-Me[e]	58.8_3	38.7_1	34.2_6	27.3_0	47.3_3	20.7_3	18.9_9
7	*cis*-2,4-di-Me	52.1_3	43.7_8	31.5_6	35.0_2	46.9_6	23.0_9	22.6_2
		(52.1_7)	(43.7_0)	(31.5_8)	(35.0_6)	(46.9_8)		
8	*trans*-2,4-di-Me	46.4_3	40.6_2	26.0_7	33.0_9	41.0_6	21.8_6	19.3_9
		(46.4_3)	40.6_1)	(26.0_7)	(33.0_9)	(41.0_6)		
9	*cis*-2,5-di-Me	51.2_2	29.9_7	29.9_1	28.4_6	51.3_2	21.7_5	17.5_1
		(51.2_9)	(29.8_9)	(30.2_4)	(28.3_7)	(51.4_1)		
10	*trans*-2,5-di-Me	51.9_7	34.8_6	33.8_9	31.7_7	54.8_2	22.7_7	19.5_3
		(51.9_0)	(34.9_6)	(33.9_9)	(31.7_8)	(54.8_6)		
11	*cis*-2,6-di-Me	52.6_2	34.2_4	25.1_0	34.2_4	52.6_2	23.1_2	23.1_2
		(52.5_0)	(34.1_7)	(25.0_8)	(34.1_7)	(52.5_0)		
12	*trans*-2,6-di-Me	46.0_7	32.9_6	19.5_5	32.9_6	46.0_7	21.0_5	21.0_5
		(46.0_4)	(32.9_9)	(19.5_5)	(32.9_9)	(46.0_4)		
13	*cis*-3,4-di-Me[e]	51.9_9	34.1_9	33.1_3	31.4_3	45.1_6	13.0_8	17.0_4
14	*trans*-3,4-di-Me[e]	54.7_9	39.3_8	38.1_9	36.0_3	47.3_7	16.9_4	19.9_4
15	*cis*-3,5-di-Me	54.1_7	32.5_7	42.9_0	32.5_7	54.1_7	19.6_5	19.6_5
		(54.2_7)	(32.5_7)	(42.9_0)	(32.5_7)	(54.2_7)		
16	*trans*-3,5-di-Me	53.4_0	27.4_5	39.5_7	27.4_5	53.4_0	18.6_3	18.6_3
		(53.2_8)	(27.6_1)	(39.5_7)	(27.6_1)	(53.2_8)		

[a] Calculated values in parentheses. [b] In parts per million from Me_4Si, solvent $CDCl_3$. [c] Methyl group attached to lower numbered carbon. [d] Methyl group attached to higher numbered carbon. [e] Calculated values agree perfectly with experimental values through choice of vicinal parameters.

Table II. Experimental and Calculated[a] Shifts for C-Methylated *N*-Methylpiperidines[b]

compd	C substituent	C(2)	C(3)	C(4)	C(5)	C(6)	C-Me[c]	C-Me[d]	N-Me
1m	none	56.6_0	26.0_7	23.8_4	26.0_7	56.6_0			46.9_3
		(56.7_4)	(26.0_7)	(23.7_7)	(26.0_7)	(56.7_4)			
2m	2-Me	59.4_1	34.8_8	24.7_3	26.4_3	57.2_2	20.4_2		43.3_7
		(58.9_2)	(34.9_5)	(24.0_3)	(26.2_5)	(57.0_2)			
3m	3-Me	64.1_7	31.2_1	32.5_3	25.6_5	56.0_0	19.7_2		46.5_9
		(64.2_1)	(31.2_1)	(32.5_1)	(25.5_9)	(56.2_7)			
4m	4-Me	56.0_7	34.4_8	30.2_3	34.4_8	56.0_7	21.8_6		46.4_9
		(56.2_5)	(34.5_1)	(30.3_8)	(34.5_1)	(56.2_5)			
5m	*cis*-2,3-di-Me[e]	60.7_5	34.8_2	29.3_7	23.5_5	52.9_1	10.8_9	15.7_1	43.4_2
6m	*trans*-2,3-di-Me[e]	66.1_6	37.2_4	34.0_6	25.7_3	57.5_7	17.1_3	19.7_6	43.5_3
7m	*cis*-2,4-di-Me	59.0_9	43.7_0	31.4_0	34.8_2	57.3_5	20.9_3	22.1_0	42.9_7
		(58.9_4)	(43.6_9)	(31.2_6)	(34.8_4)	(57.3_3)			
8m	*trans*-2,4-di-Me	(53.5_6)	40.7_7	25.2_0	33.2_7	49.5_5	14.6_5	20.1_5	43.0_8
		(53.8_5)	(40.6_9)	(25.1_8)	(33.4_6)	(49.1_9)			
9m	*cis*-2,5-di-Me	56.4_8	30.8_6	28.6_8	30.1_8	59.2_9	14.1_2	18.9_1	43.4_2
		(56.8_5)	(30.8_2)	(28.9_9)	(30.1_4)	(59.6_8)			
10m	*trans*-2,5-di-Me	59.1_1	34.9_6	33.6_8	31.6_3	65.3_6	20.6_2	19.6_7	43.2_6
		(58.6_4)	(34.9_2)	(33.2_3)	(31.5_4)	(65.1_0)			
11m	*cis*-2,6-di-Me	59.5_9	35.1_7	24.7_9	35.1_7	59.5_9	21.6_2	21.6_2	38.0_7
		(59.8_8)	(35.2_8)	(24.8_6)	(35.2_8)	(59.8_8)			
12m	*trans*-2,6-di-Me	52.9_6	33.6_5	19.3_0	33.6_5	52.9_6	15.1_3	15.1_3	40.0_8
		(53.0_5)	(33.7_7)	(19.3_1)	(33.7_7)	(53.0_5)			
13m	*cis*-3,4-di-Me[e]	61.1_1	33.9_0	30.7_8	31.8_3	54.0_8	14.3_1	15.8_3	46.7_9
14m	*trans*-3,4-di-Me[e]	64.1_6	37.8_5	37.0_5	34.8_8	56.4_7	17.1_9	19.3_1	46.4_4
15m	*cis*-3,5-di-Me	63.5_9	31.1_0	41.6_1	31.1_0	63.5_9	19.5_5	19.5_5	46.2_1
		(63.8_6)	(31.1_8)	(41.6_1)	(31.1_8)	(63.8_6)			
16m	*trans*-3,5-di-Me	63.3_2	27.3_7	38.4_5	27.3_7	63.3_2	19.2_5	19.2_5	47.0_0
		(62.8_9)	(27.4_2)	(38.4_5)	(27.4_2)	(62.8_9)			
17m	*r*-2,*c*-4-*c*-6-tri-Me	59.3_1	43.8_3	30.9_4	43.8_3	59.3_1	21.5_6[f]	22.0_9	37.8_8
		(59.7_1)	(43.8_7)	(31.8_0)	(43.8_7)	(59.7_1)			
18m	*r*-2,*t*-4,*c*-6-tri-Me	53.3_1	40.9_4	26.1_8	40.9_4	53.3_1	21.5_2[f]	18.6_1	38.1_4
		(53.3_4)	(40.8_9)	(25.1_0)	(40.8_9)	(53.3_4)			
19m	*r*-2,*c*-4,*t*-6-tri-Me	56.0_4	40.8_7	25.2_8	43.9_8	50.0_7	9.7_1	22.4_6[g]	39.6_6
		(55.7_0)	(40.8_7)	(26.2_5)	(43.8_5)	(50.0_5)			

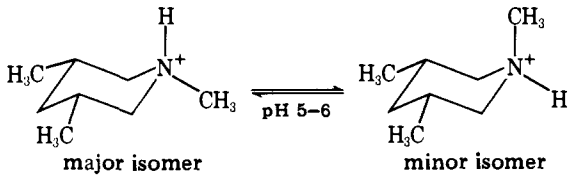
[a] Calculated values in parentheses. [b] In parts per million from Me_4Si, solvent $CDCl_3$. [c] Methyl group attached to lower numbered carbon. [d] Methyl group attached to higher numbered carbon. [e] Calculated values agree perfectly with experimental values through choice of vicinal parameters. [f] Double intensity signal. [g] Also signal at 21.32 ppm for Me(6).

Table III. ^{13}C Substituent Parameters (ppm) in C-Methylated Piperidines and *N*-Methylpiperidines in Chloroform-*d*

effect	piperidine, position[a,b]			*N*-methylpiperidine, position[a,b]		
	C(2)	C(3)	C(4)	C(2)	C(3)	C(4)
base value	47.6_1	27.3_7	25.3_0	56.7_4	26.0_7	23.7_7
α_e	5.04 (8)	5.33 (11)	6.39 (5)	2.4 (2)	5.29 (9)	6.95 (18)
α_a	−1.11 (33)	0.94 (18)	0.89 (8)	−1.63 (38)	2.75 (21)	0.25 (46)
β_e	7.40 (9)	7.72 (9)[c] 8.60 (10)[d]	8.80 (3)	7.59 (32)	9.03 (7)[c] 8.59 (7)[d]	8.92 (12)
β_a	4.73 (15)	4.61 (40)[c] 5.53 (15)[d]	5.47 (6)	5.64 (73)	6.02 (11)[c] 5.61 (11)[d]	5.75 (20)
γ_e	−0.48 (9)[d] −0.15 (8)[e]	−0.13 (11)	−0.11 (3)	−0.17 (24)[d] 0.77 (23)[e]	−0.18 (9)	0.54 (10)
γ_a	−6.05 (13)[d] −6.92 (33)[e]	−5.66 (18)	−5.64 (6)	−6.55 (39)[d] −8.89 (38)[e]	−5.17 (21)	−5.01 (20)
δ_e	−0.75 (9)	−0.92 (9)		−0.47 (32)	0.18 (16)	
δ_a	−0.05 (15)	−0.17 (40)		−0.46 (73)	0.16 (11)	
$vic_{2,3}^{cis}$	-2.4_5[f]	-3.0_6[g]	1.3_2	-3.1_7[n]	-2.8_4[o]	$+0.2_8$
$vic_{2,3}^{trans}$	-1.2_2[h]	-1.7_1[i]	0.2_7	-0.5_5[p]	-3.1_5[q]	0.8_3
$vic_{3,4}^{cis}$	1.2_0[j]	-3.2_2[k]	-3.2_4	0.5_0[r]	-3.3_6[s]	-4.4_6
$vic_{3,4}^{trans}$	0.2_5[l]	-1.9_3[m]	-2.3_0	7.0_3[t]	-2.9_2[u]	-2.5_9

[a] Carbon observed. [b] Values in parentheses are standard deviations of the last decimal given. [c] From C(2). [d] From C(4). [e] From C(6). [f] Value at C(6): 0.19. [g] Value at C(5): 0.27. [h] Value at C(6): 0.62. [i] Value at C(5): 0.98. [j] Value at C(6): 0.40. [k] Value at C(5): 0.21. [l] Value at C(6): 0.98. [m] Value at C(5): 0.19. [n] Value at C(6): −0.17. [o] Value at C(5): 0.43. [p] Value at C(6): 0.54. [q] Value at C(5): −0.35. [r] Value at C(6): 0.21. [s] Value at C(15): 1.64. [t] Value at C(6): 0.38. [u] Value at C(5): 0.40.

Scheme I



major isomer minor isomer

The piperidine and, separately,[27] the *N*-methylpiperidine data were subjected to multiple linear regression analysis[28] to determine optimal substitution parameters which are summarized in Table III. (The vicinal parameters generally occur only once and were calculated by hand.) The shifts given in parentheses in Tables I and II are the calculated shift values; agreement with experiment is generally excellent if to some extent overstated inasmuch as the number of parameters is large relative to the number of data. For those compounds which are conformationally heterogeneous (e.g., *cis*-2,5-dimethylpiperidine) the shifts were calculated[29] as $n_e\delta_e + n_a\delta_a$ where n_e and n_a are the mole fractions of equatorial and axial conformations (with respect to a specified methyl group) as determined by conformational analysis (see below) and δ_e and δ_a are the chemical shifts under study in the pure conformational isomers as determined from the regression analysis.

The hydrochlorides of the *N*-methyl compounds were studied at a pH high enough to allow equilibration of the two stereoisomers (e.g., Scheme I) on the laboratory time scale but not so high as to lead to coalescence on the NMR time scale. To this end the pH was gradually raised until coalescence of the peaks of the two diastereomeric salts (Scheme I) occurred in the ^{13}C NMR spectrum. At that pH it may be estimated that the rate of interconversion of the isomeric salts (proceeding via the free amines) is of the order of 100 s^{-1}, the separation of the peaks of the stereoisomers being, in a number of cases, of the order of 100 Hz. Lowering the pH by 2–3 units (to about 5–6) will restore the spectra of the individual diastereomers (since their interconversion is now slow on the NMR time scale) but will ensure that the diastereomers are still in equilibrium, since their rate of interconversion has been retarded by only two to three powers of ten, so that their half-life is of the order of seconds or tens of seconds. That this condition (rapid equilibration of diastereomers on the laboratory time scale) remain fulfilled is important for the observation of the equilibrium of axial and equatorial NCH_3 groups in the piperidinium salts (vide infra), although from the point of view of ^{13}C NMR spectroscopy all that matters is that both species be present and not be interconverted rapidly on the NMR time scale.

The chemical shifts of the *N*-methylpiperidinium hydrochlorides (in D_2O) are listed in Table IV. For the sake of convenience, the hydrochlorides in Table IV are keyed with the same numbers as the free amines in Table II; since most *N*-methylpiperidines give rise to two hydrochlorides, these are distinguished by the letters E (for equatorial or more largely equatorial *N*-methyl) and A (for axial or more largely axial *N*-methyl). Because of the limited amount of data available, we did not attempt to calculate substitution parameters for the salts.

Conformational Analysis. For the conformational analysis of the free piperidines, *N*,3-dimethylpiperidine (**3m**) and the conformationally mobile dimethyl compounds *cis*-2,3- (**5**), *trans*-2,4- (**8**), *cis*-2,5- (**9**), and *cis*-3,4-dimethylpiperidine (**13**) (Scheme II, R = H) and their *N*-methyl homologues **5m**, **8m**, **9m**, and **13m** (Scheme II, R = Me) were subjected to ^{13}C NMR spectroscopy at temperatures of −80 to −95 °C, i.e., well below the coalescence temperature. The chemical shifts of the various compounds at low temperature are shown in Table V. There was no difficulty in assigning shifts to conformational isomers by using the substitution parameters in Table III[30] and making use of the fact that the amounts of the two conformations were, in all cases, unequal. The proportions of the conformational isomers were determined by integration of the italicized peaks, with the equilibrium constants and corresponding free-energy values reported in Table VI. There is always a question whether such ratios in ^{13}C spectra may be distorted by unequal relaxation times and unequal nuclear Overhauser effects; we have minimized the chances of errors due to this source by comparing the integrals of corresponding peaks (e.g., C-2 in one conformer with C-2 in the other), by endeavoring, insofar as possible, to integrate several pairs (with consistent results) and by spot-checking the method by integrating known mixtures of *configurational* isomers (e.g., *cis*- and *trans*-2,4-dimethylpiperidine).[31] As a result we believe such errors not to exceed 20% in *K*, i.e., less than 0.1 kcal/mol in $\Delta G°$, except possibly for **3m**.

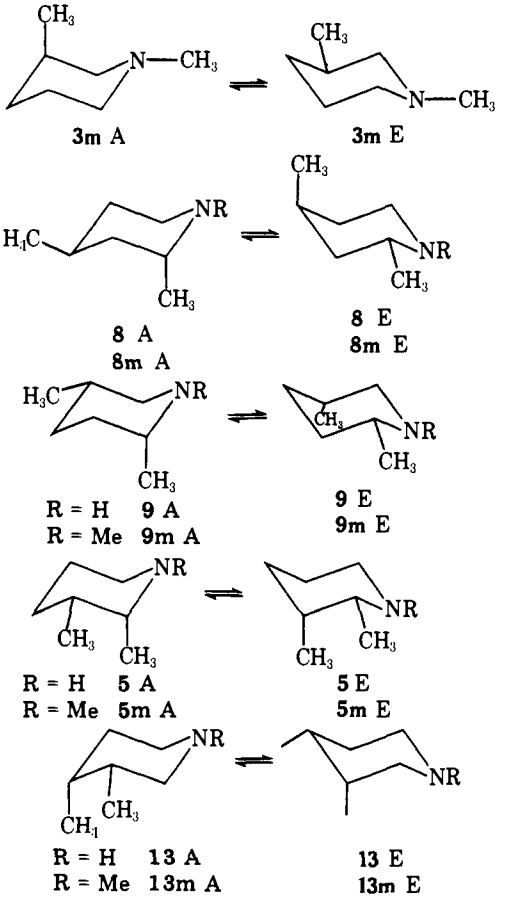
The conformational equilibrium for **3m** directly yields the conformational energy of methyl at C(3) in *N*,3-dimethylpiperidine. Unfortunately the equilibrium is quite one-sided at −100 °C (99:1) and the accuracy of the measurement correspondingly low; as a result there may be sizable errors in the

Table IV. ^{13}C Chemical Shifts in *N*-Alkylpiperidinium Hydrochloride Salts[a,b]

substituent	hydrochloride of	C(2)	C(3)	C(4)	C(5)	C(6)	Me[d]	Me[e]	N-Me
1-Me	**1m**	55.2$_7$	23.7$_9$	21.8$_7$	23.8$_7$	55.2$_7$			44.2$_9$
trans-1,2-di-Me	**2m**, E*	*62.5*$_6$	*32.4*$_6$	*22.6*$_9$	*24.2*$_2$	*56.8*$_6$	*18.2*$_7$		*41.4*$_8$
cis-1,2-di-Me	**2m**, A	*58.1*$_8$	*28.0*$_0$	*19.1*$_9$	*21.1*$_7$	*51.7*$_3$	*13.8*$_8$		*37.0*$_7$
cis-1,3-di-Me	**3m**, E*	*61.1*$_3$	(*30.1*$_0$)	(30.3$_2$)	*23.8*$_1$	*55.1*$_9$	*18.8*$_0$		*44.2*$_6$
trans-1,3-di-Me	**3m**, A	*59.4*$_9$	*28.6*$_5$	*f*	(*25.8*$_4$)	*54.3*$_7$	*17.6*$_2$		*42.2*$_3$
trans-1,4-di-Me	**4m**, E*	*55.6*$_7$	*32.1*$_1$	*28.4*$_8$	*32.1*$_1$	*55.6*$_7$	*21.3*$_9$		*44.0*$_6$
cis-1,4-di-Me	**4m**, A	*51.6*$_0$	*28.1*$_6$	*25.7*$_2$	*28.1*$_6$	*51.6*$_0$	*18.5*$_0$		*41.7*$_4$
r-,*c*-3,*c*-5-tri-Me	**15m**, E*	*60.5*$_9$	*30.0*$_8$	38.9$_8$	*30.0*$_8$	*60.5*$_9$	18.7$_2$		*44.1*$_9$
r-1,*t*-3,*t*-5-tri-Me	**15m**, A	*57.8*$_3$	*24.3*$_9$	38.9$_8$	*24.3*$_9$	*57.8*$_3$	18.8$_4$		*40.0*$_4$
r-1,*t*-2,*t*-4,tri-Me	**7m**, E*	*62.2*$_9$	40.7$_8$	29.6$_0$	32.2$_5$	*56.8*$_3$	18.2$_7$	21.4$_7$	41.2$_3$
r-1,*c*-2,*c*-4-tri-Me	**7m**, A	*58.7*$_0$	40.1$_8$	29.7$_8$	25.9$_3$	*54.6*$_3$	(18.2$_7$)	(18.0$_4$)	33.8$_6$
r-1,*c*-2,*t*-4-tri-Me	**8m**, A*	59.1$_3$	*39.6*$_2$	*24.2*$_5$	*33.3*$_6$	*50.6*$_7$	*12.6*$_9$	*22.8*$_6$	*42.3*$_1$
r-,*t*-2,*c*-4-tri-Me	**8m**, E	59.1$_3$	*38.2*$_3$	*26.1*$_4$	*30.3*$_7$	*52.4*$_6$	(*19.5*$_0$)	(*19.6*$_3$)	*42.7*$_0$
r-1,*c*-2,*c*-5-tri-Me	**9m**, E*	*54.2*$_1$	30.4$_4$	24.8$_1$	29.7$_1$	*56.5*$_3$	*9.9*$_9$	*18.7*$_6$	*41.3*$_5$
r-1,*t*-2,*t*-5-tri-Me	**9m**, A	*18.6*$_7$	*f*	*f*	*f*	*61.0*$_2$	(*17.5*$_0$)	(*17.2*$_5$)	*41.6*$_5$
r-1,*t*-2,*t*-6-tri-Me	**11m**, E*	*63.1*$_4$	*32.9*$_2$	22.7$_4$	*32.9*$_2$	*63.1*$_4$	*18.8*$_6$		*37.3*$_9$
r-1,*c*-2,*c*-6-tri-Me	**11m**, A	*60.9*$_1$	*24.9*$_9$	22.8$_8$	*24.9*$_9$	*60.9*$_1$	*18.0*$_2$		*25.2*$_3$
r-1,*c*-3,*c*-4-tri-Me	**13m**, E*	55.7$_9$	(*32.8*$_2$)	(*30.7*$_1$)	*28.8*$_2$	49.9$_5$	*16.1*$_8$	*10.7*$_0$	*43.9*$_9$
r-1,*t*-3,*t*-4-tri-Me	**13m**, A	61.3$_4$	(*32.0*$_6$)	(*30.9*$_3$)	*26.2*$_1$	55.5$_6$	*11.1*$_9$	*18.3*$_7$	*44.2*$_9$
r-1,*c*-2,*t*-4,*t*-6-tetra-Me	**19m**, E*	*59.6*$_3$	*38.3*$_2$	*23.8*$_4$	*41.0*$_3$	*55.1*$_1$	*11.3*$_2$	*21.5*$_3$[g]	*38.7*$_9$
r-1,*c*-2,*c*-4,*t*-6-tetra-Me	**19m**, A	*52.1*$_1$	(*34.0*$_2$)	*24.2*$_3$	*31.3*$_1$	*60.0*$_9$	*17.6*$_8$	*19.3*$_4$[h]	(*34.1*$_6$)
cis-1-*t*-Bu-3-Me*	(A*)	53.5$_0$	30.3$_3$	*30.9*$_2$	23.7$_9$	47.5$_9$	*19.2*$_2$	24.8$_4$[i]	64.0$_8$[j]
trans-1-*t*-Bu-3-Me	(A)	47.7[k]	*f*	*29.0*[k]	21.1[k]	*f*	*16.8*[k]	*f*	*f*
cis-1-*t*-Bu-4-Me	(A)	*43.0*$_7$	29.4$_4$	23.5$_1$	29.4$_4$	*43.0*$_7$	*16.5*$_0$	25.0$_1$[k]	63.9$_0$[j]
trans-1-*t*-Bu-4-Me	(E*)	*48.0*$_5$	32.2$_2$	29.2$_2$	32.2$_2$	*48.0*$_5$	*21.4*$_5$	25.0$_1$[i]	63.9$_0$[j]

[a] In D_2O, measured from 1,4-dioxane, δ = 67.4 ppm, referred to Me_4Si. [b] Assignments in parentheses are uncertain. [c] More stable isomer starred. [d] Methyl group attached to lower numbered carbon. [e] Methyl group attached to higher numbered carbon. [f] Not seen or uncertain. [g] Also Me(6) peak at 18.07 ppm. [h] Also Me(6) peak at 16.50 ppm. [i] *Me*$_3$C. [j] Me$_3$*C*. [k] Approximate values.

Scheme II



$\Delta G°$ value for 3-Me in **3m** and in all the other values derived therefrom (but see below). We have used the same value (1.6 kcal/mol) determined for **3m** also for the corresponding NH compound **3**; it appeared that the error so committed would be less than the uncertainty introduced in a low-temperature measurement on **3** itself which may be subject to intermolecular hydrogen bonding and association especially at −90 °C.

If one reasonably assumes[33] that conformational energies are additive for nonvicinal substituents, equilibrium data for **9** and **9m** (Table VI) along with those for **3m** permit calculation of the conformational energy for a 2-methyl substituent in piperidine and *N*-methylpiperidine. Once the latter value is known, data for **8** and **8m** in turn permit calculation of the conformational energy for a 4-methyl group. The pertinent values are summarized in Table VII. The value for Me-3 in *N*,3-dimethylpiperidine is in fair agreement with that (1.51 kcal/mol) reported earlier;[8b] the discrepancy from the reported[8b] value for *N*,4-dimethylpiperidine (1.98 kcal/mol) is somewhat greater; the difference we compute between Me-3 and Me-4 (0.2 kcal/mol) is significantly less than that (0.47 kcal/mol) reported,[8b] especially if one takes into account that the accuracy of differences between $\Delta G°$ values in our work is considerably greater than that of the absolute values (vide supra). It is particularly gratifying that our value for the 4-methyl group in piperidine—1.9 kcal/mol—is in excellent agreement with Booth's of 1.93 ± 0.02 kcal/mol,[15] which should be quite accurate since it was determined with ^{13}C-enriched substrate. This internal consistency enhances one's confidence in our measured value for *N*,3-dimethylpiperidine (**3m**) and in our assumption that the same value would hold also for 3-methylpiperidine.

In the case of the amine salts, only those derived from *N*-methylpiperidines were investigated. Since, as mentioned above, nitrogen inversion in the salts is slow on the NMR time scale at pH values in the 5-6 region, equilibria of the type shown in Scheme I can be observed and evaluated directly by integration of the pertinent ^{13}C signals (italicized in Table IV) of the two stereoisomers (configurational or cis-trans isomers in this case). For more complex equilibria such as that shown in Scheme III, the cis/trans ratio—but not, of course, the ratio of the two conformations of the cis isomer—can be evaluated directly from the room-temperature ^{13}C spectrum. Pertinent equilibrium constants and free-energy differences are tabulated

Table V. ^{13}C Chemical Shifts of Piperidines (**5, 8, 9, 13**) and *N*-Methylpiperidines (**3me, 5me, 8me, 9me, 13me**) at −80 to −95 °C in CD_2Cl_2 (NH) or $CHCl{=}CCl_2/CD_3COCD_3$ (NMe)[a]

no.	conformation	C(2)	C(3)	C(4)	C(5)	C(6)	Me_A[b]	Me_B[c]	N-Me
5	E[d]	54.6$_9$	*32.6$_9$*	32.5$_1$	(20.8$_8$)	*47.8$_6$*	(20.6$_6$)	11.4$_7$	
	A[e]	51.9$_1$	*34.8$_5$*	(27.1$_9$)	27.3$_9$)	*38.9$_4$*	12.2$_2$	19.9$_4$	
8	E[d]	*46.0$_0$*	(41.3$_4$)	26.5$_6$	31.3$_5$	(40.1$_2$)	23.4$_5$	17.9$_1$	
	A[e]	*47.2$_7$*	(39.5$_7$)	25.1$_7$	35.6$_0$	(41.3$_4$)	*f*	22.9$_6$	
9	E[d]	(*52.2$_8$*)	(30.4$_3$)	(29.3$_7$)	(27.3$_0$)	(*53.0$_6$*)	23.2$_9$	16.9$_6$	
	A[e]	(*46.1$_8$*)	31.0$_2$	27.6$_9$	32.9$_0$	(*46.9$_8$*)	f	20.1$_1$	
13	E[d]	53.2$_7$	33.6$_7$	33.2$_4$	*29.0$_2$*	47.0$_3$	11.1$_3$	20.4$_3$	
	A[e]	46.4$_8$	34.0$_9$	34.0$_9$	*31.0$_6$*	39.5$_3$	17.4$_4$	11.3$_6$	
3me	E[d]	63.8$_2$	31.2$_1$	32.3$_8$	25.6$_1$	55.7$_3$	20.0$_8$		46.6$_5$
	A[e]	61.6$_3$	28.2$_4$	28.8$_8$	22.2$_0$	*f*	18.8$_7$		*f*
5me	E[d]	*62.1$_8$*	*34.8$_2$*	32.6$_3$	21.4$_0$	*58.3$_5$*	*19.4$_1$*	*12.7$_4$*	43.6$_2$
	A[e]	*58.8$_2$*	*35.2$_4$*	(26.1$_3$)	(26.2$_2$)	*46.7$_0$*	*1.7$_9$*	*19.6$_3$*	43.1$_7$
8me	E[d]	*53.3$_5$*	40.6$_1$	*26.4$_7$*	*31.6$_1$*	*51.3$_9$*	*21.2$_3$*	*17.7$_3$*	*43.3$_6$*
	A[e]	*53.6$_0$*	40.6$_1$	*24.3$_3$*	*34.8$_2$*	*47.3$_1$*	*8.0$_6$*	*22.7$_9$*	*42.8$_7$*
9me	E[d]	*60.4$_4$*	31.7$_6$	*30.4$_0$*	29.0$_3$	*62.9$_1$*	*21.0$_4$*	*18.0$_3$*	*43.7$_1$*
	A[e]	*52.6$_8$*	29.8$_3$	*26.9$_5$*	31.7$_6$	*55.1$_2$*	*7.3$_2$*	*20.1$_1$*	*42.9$_5$*
13me	E[d]	*63.3$_6$*	34.0$_6$	33.1$_2$	28.7$_8$	*56.8$_7$*	*12.4$_5$*	*19.7$_6$*	*46.8$_7$*
	A[e]	*57.2$_5$*	33.6$_7$	32.9$_3$	30.2$_5$	*49.77*	*17.3$_8$*	*11.3$_5$*	*46.5$_2$*

[a] Shifts in parts per million from Me_4Si. [b] Lower numbered CH_3 group (Me_2 or Me_3). [c] Higher numbered CH_3 (Me_3, Me_4, or Me_5). [d] Major conformer. [e] Minor conformer. [f] Peak not clearly seen.

Table VI. Conformational Equilibria at Low Temperature

conformers	5E/5A	8E/8A	9E/9A	13E/13A	3mE/3mA	5mE/5mA	8mE/8mA	9mE/9mA	13mE/13mA
K_{av}	10.0[a]	4.55[b]	9.7[c]	2.4[a]	99.0[d]	1.76[c]	0.80[c]	1.36[c]	2.68[c]
$-\Delta G°$[e]	0.84	0.54	0.87	0.32	1.6	0.22	−0.09	0.12	0.38

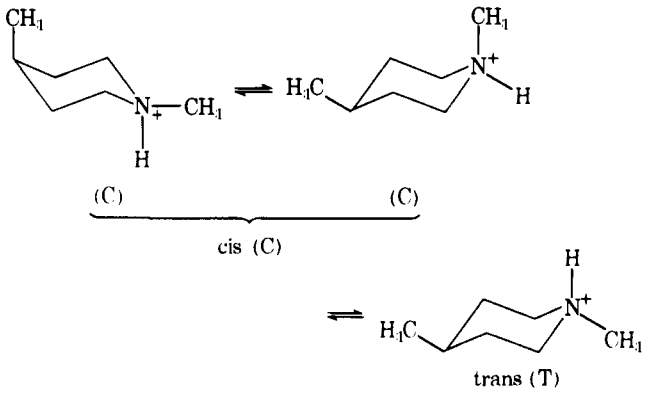
[a] At −90 °C. [b] At −95 °C. [c] At −80 °C. [d] At −100 °C. [e] In kcal/mol.

Table VII. Conformational Free Energies for Methyl Groups in Piperidine Systems[a]

	Me-2	Me-3	Me-4	N-Me
piperidines	2.5	1.6[b]	1.9[c]	
N-methylpiperidines	1.7	1.6[d,e]	1.8	2.4[10]
N-methylpiperidinium hydrochlorides	1.4	2.2[f]	1.6	2.1

[a] In kcal/mol. [b] Assumed. [c] Reported[15] 1.93 kcal/mol. [d] Reported[8b] 1.51 kcal/mol. [e] In taking this value directly from Table VI, we are disregarding the conformation of the cis isomer in which the N-Me is axial and the C-Me equatorial. Since $\Delta G°$ = 2.41 kcal/mol for the *N*-methyl group in *N*-methylpiperidine,[10] K = 1/1101 at −100 °C and it can be easily shown that inclusion of the N-Me axial conformation will not palpably alter $-\Delta G°_{Me}$. [f] Not known with accuracy; values fluctuate from 1.82 to 2.57 kcal/mol. See text.

Scheme III



in Table VIII; we shall return to an evaluation of these data in the sequel.

Table VIII. Equilibrium Parameters for Stereoisomeric (Cis-Trans) Pairs of *N*-Methylpiperidinium Hydrochlorides in D_2O[a]

entry	compd	C substituents	K	$-\Delta G°$, kcal/mol
1	**2m**·HCl	2-Me	5.7	1.03 ± 0.04
2	**3m**·HCl	3-Me	17.25	1.74 ± 0.04
3	**4m**·HCl	4-Me	10.1	1.37 ± 0.05
4	**15m**·HCl	*cis*-3,5-di-Me	30.4	2.09 ± 0.02
5	**7m**·HCl	*cis*-2,4-di-Me	11.2	1.41 ± 0.06[b]
6	**9m**·HCl	*cis*-2,5-di-Me	1.63	0.30 ± 0.01
7	**13m**·HCl	*cis*-3,4-di-Me	1.35	0.19 ± 0.03
8	**11m**·HCl	*cis*-2,6-di-Me	2.11	0.44 ± 0.04[c]
9	**8m**·HCl	*trans*-2,4-di-Me	1.24	0.13 ± 0.05
10	**19m**·HCl	*r*-2,*c*-4,*t*-6-tri-Me	4.0	0.85 ± 0.05

[a] At 35 °C. [b] Reported[42] 0.82 kcal/mol. [c] Reported 0.36, 0.39;[42] 0.17;[43] ca. 0.41 kcal/mol.[44]

Discussion

Conformational Analysis of *C*-Methylpiperidines. The pertinent data are contained in Table VII. The 1.6 kcal/mol value for *N*,3-dimethylpiperidine was obtained by direct NMR measurements at low temperature; possible imprecision of this value has been discussed above. The value for 3-methylpiperidine was assumed to be the same. Both values are slightly smaller than the 1.7 kcal/mol[33,34] value for axial methylcyclohexane, but the difference is somewhat less than might have been expected, considering that in axial 3-methylpiperidines the methyl group is syn-axial with only one hydrogen atom plus the lone pair on nitrogen whereas in axial methylcyclohexane it is syn-axial with two hydrogen atoms. The *H*-C-C-C-*N*: syn-axial interaction has recently been evaluated,[35] from the conformational equilibrium in *cis*-decahydroisoquinoline, to amount to 0.53 kcal/mol. If one assumes that this is equal to the interaction of an axial 3-Me with the nitrogen in 3-methylpiperidine, and if one takes the interaction of the axial methyl group with CH_2(5) as 0.87 kcal/mol (i.e., one-half the value for axial methylcyclohexane[34]), the calculated $-\Delta G°$ for 3-Me is 0.53 + 0.87 = 1.4 kcal/mol; thus the experimental value is slightly larger, but perhaps within the limits of uncertainty of the experiment and the calculation.

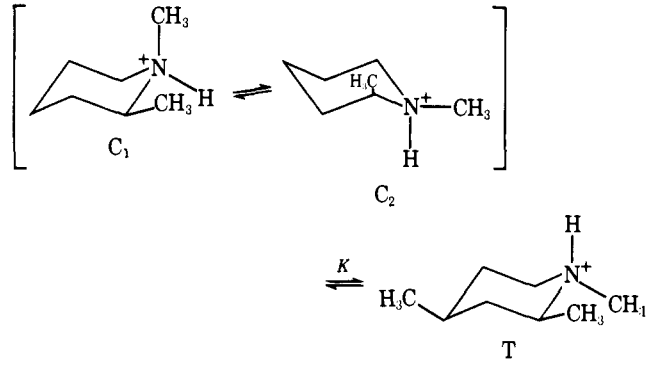
From the 3-methylpiperidine value and the equilibria for the *cis*-2,5-dimethylpiperidines (**9**, **9m**, Table VI) the $-\Delta G°$ values for 2-methyl groups in 2-methylpiperidine and *N*,2-dimethylpiperidine (Table VIII) may be computed, assuming additivity of the free-energy changes involved in moving the 2- and 5-methyl groups between equatorial and axial positions. The two values are quite different. The one for 2-methylpiperidine (2.5 kcal/mol) is remarkably large. This may be because the relatively short C-N bond distance (1.47 Å vs. 1.54 Å for C-C) leads to a correspondingly short nonbonded distance between the axial 2-Me group and the syn-axial hydrogen at C(6). A similar situation has been found in axially 2-substituted 1,3-dioxanes.[36] If one accepts this argument, then the much reduced $-\Delta G°$ value (1.7 kcal/mol, "normal" by cyclohexane standards) for 2-Me in *N*,2-dimethylpiperidine comes as a surprise. We had postulated in our preliminary communication[14] that the *N*-methyl group destabilizes the equatorial Me-2 group vis-à-vis the axial because, as a result of the assumed puckering of the ring in the C(6)-N-C(2)-C(3) region, N-Me and equatorial 2-Me are closer together than N-Me and axial 2-Me. This would lead to a reduction in $-\Delta G°$, inasmuch as the axial 2-methyl group in *N*,2-dimethylpiperidine would be less disfavored, relative to an equatorial methyl group, in *N*,2-dimethylpiperidine than in 2-methylpiperidine itself.[37] However, this hypothesis is not supported by force-field calculations[38] and is not in agreement with crystal-structure data of *N*-methylpiperidinium chlorides in the literature. Thus, from the available[39] structural data for *r*-1,*t*-2,*t*-6-trimethylpiperidinium chloride (all methyl groups equatorial), we have calculated internal torsional angles about the N-C(2) and N-C(6) bonds of −57.7 and 57.2°, respectively, very close to the corresponding torsional angles (range 56.3-58.1°) found in unsubstituted piperidinium salts.[40] A slightly more puckered situation is found in an N,2-disubstituted piperidine[41] (free base), but even here, though the torsional angle around the N-C(6) bond is −61.4°, that around the salient N-C(2) bond, 59.4°, falls short of the ideal chair angle of 60° and thus provides no support for the puckering hypothesis. The various pieces of evidence that a cis-N,2 interaction of methyl group in piperidine and its salts is less than the corresponding trans-N,2 interaction thus remain without rational explanation.

From the 2-methylpiperidine equilibria and those of *trans*-2,4-dimethylpiperidines (**8**, **8m**, Table VI) one calculates the $-\Delta G°$ values for 4-methylpiperidine and *N*,4-dimethylpiperidine (Table VII). The values (1.9 and 1.8 kcal/mol) appear somewhat larger than the cyclohexane value, but the difference is within experimental error.

The data for the 2,3- and 3,4-dimethylpiperidines and their *N*-methyl analogues (Table IV) indicate that the $\Delta G°$ values in these compounds are nearly additive: **5**, 0.84 (0.9), **5m**, 0.22 (0.1), **13**, 0.32 (0.3), **13m**, 0.38 (0.2) (additive values are computed from Table VIII and shown in parentheses). For the NH compounds there are thus no palpable differences between Me-2e/Me-3a and Me-2a/Me-3e or Me-3e/Me-4a and Me-3a/Me-4e interactions; for the N-Me compounds such differences do not exceed 0.2 kcal/mol.

Conformational Analysis of Amine Salts. Of greatest interest is the *N*-methyl equilibrium value for *N*,*cis*-3,5-trimethylpiperidinium hydrochloride (Table VIII, entry 4). The $-\Delta G°$, 2.09 kcal/mol, is unquestionably smaller that for the corresponding free amine (2.4-3.0 kcal/mol[8]). If there are any doubts about this point at all (large $-\Delta G°$ values are notoriously hard to measure accurately), they are laid to rest by examining corresponding values for the salts of **7m** (entry 5) and **11m** (entry 8), which are greatly attenuated relative to the values of the free amines. For example, $-\Delta G°$ for **11m** (free amine), 1.84 kcal/mol as measured by Robinson's quenching method,[10] is unquestionably larger than the easy-to-measure

Scheme IV



value of 0.44 kcal/mol for the hydrochloride. The salt value is in agreement with those found by ^1H NMR in several other laboratories[42-45] and for the free amine **11m** we have independently found that $-\Delta G° > 1.3$ kcal/mol.[46]

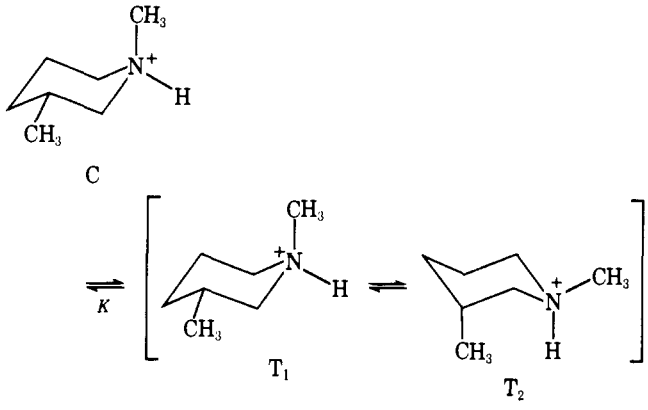
That the N-methyl group in *N*-methylpiperidinium salts has a lesser tendency to be equatorial than in the free piperidines comes, at first sight, as a surprise. One might have expected that relief of strain by outward bending of the methyl group would be easier in the free amine than in the salt because of lack of buttressing in the latter. Clearly this factor is not dominant.

We can envisage two factors stabilizing the axial N-Me conformation in the salts over that in the amines. One is solvation: it is known that amine salts are solvated mostly from the side or sides of the protons attached to nitrogen.[47] Thus the equatorially protonated salt (axial Me) should be stabilized by solvation relative to the axially protonated one (equatorial Me) since solvation is known from other data ($-\Delta G°$ values of cyclohexylammonium salts vs. those of the free amines or of cyclohexanecarboxylate salts vs. those of the free carboxylic acid[48]) to be easier from the equatorial than from the axial side. Another possibility is that differences in bond length cause steric effects in the amine salts to be less than those in the free amines. Thus the C(2)-N and C(6)-N bond lengths in **11m**[39] (equatorial N-Me), 1.517 and 1.516 Å, are longer than the standard[49] C-N bond length in amines, 1.472 Å, and virtually identical with the C(2)-C(3) and C(5)-C(6) bond lengths (1.519, 1.512 Å). Further work is required to sort out these factors.

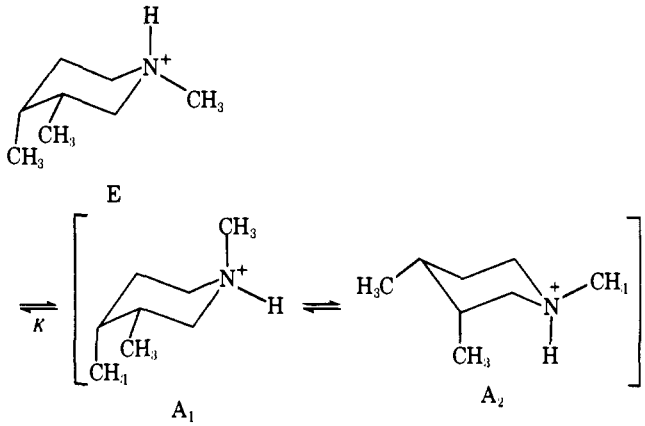
The $-\Delta G°$ values for *N*,*cis*-2,4- (entry 5) and *N*,*cis*-2,6-trimethylpiperidinium (entry 8) salts are considerably lower than those for the cis-3,5 isomer discussed above, as had been established earlier by ^1H NMR spectroscopy.[42-45] We have alluded to this point earlier: it suggests that the additional equatorial/equatorial N-Me/C-Me gauche interactions in **7m**·HCl (entry 5) and **11m**·HCl (entry 8) are more severe than corresponding axial/equatorial N-Me/C-Me. The resulting reduction in the conformational energy of the N-Me group amounts to 0.6 kcal/mol in **7m** (compared to **15m**, entry 4) and an additional 1.0 kcal/mol for the second group in **11m**. As stated above, the reason for these substantial reductions is not obvious;[50] the situation found in piperidinium salts is the exact opposite of that found earlier in thianium salts[51] where the conformational energy of the *S*-methyl group is *enhanced* by buttressing substituents at C(2) and C(6).

The $-\Delta G°$ value for **2m**·HCl (entry 1) is related to that for the cis-2,4 homologue (entry 5) as shown in Scheme IV. The equilibrium constant K for **2m**·HCl is equal to $T/(C_1 + C_2)$ whence $1/K = 1/K_1 + 1/K_2$, K_1 and K_2 being the equilibrium constants as between T and C_1 and C_2 individually. K_1 may be taken as equal to the value for **7m**·HCl, i.e., 11.2 and, since $K = 5.7$, it follows that K_2 (=T/C_2) is 11.6 and $\Delta G° = -1.45$ kcal/mol. Thus $\Delta G°$ for the 2-methyl group in an *N*,2-dimethylpiperidinium salt (in which the N-Me group is fixed in

Scheme V



Scheme VI

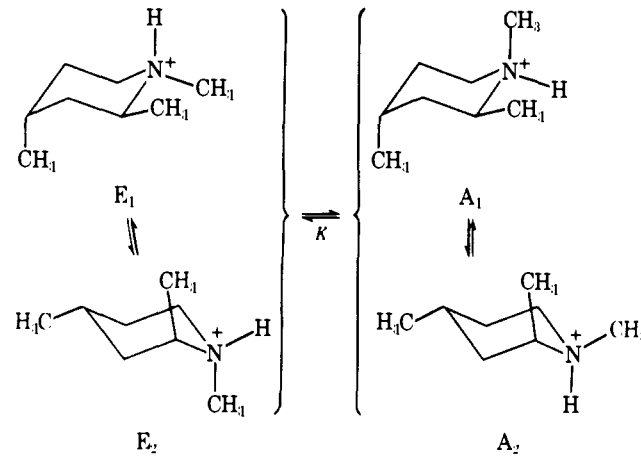


the equatorial position) is less than the value of 1.7 kcal/mol in the free *N*,2-dimethylpiperidine (Table VII).

The $-\Delta G°$ values of *N*,3- and *N*,4-dimethylpiperidinium salts (entries 2 and 3) may be compared to those for *N-tert*-3-methyl- (2.57 kcal/mol) and *N-tert*-butyl-4-methylpiperidinium salts (1.65 kcal/mol). The latter two values should represent the conformational energies of 3-Me and 4-Me groups, respectively, in the salts. Scheme V displays the situation for *N*,3-dimethylpiperidinium hydrochloride and an exactly analogous equilibrium scheme applies to the N,4 isomer. According to Scheme V, $K = C/(T_1 + T_2)$ or $1/K = T_1/C + T_2/C$. Assuming the absence of buttressing effects, T_1/C may be taken from the data for *N*,3,5-trimethylpiperidinium chloride (Table VIII, entry 4) as 1/30.6 and, since K = 17.25 (entry 2), T_2/C = 0.025; i.e., the equilibrium constant for the 3-Me group in **3m**·HCl is 39.5 and $-\Delta G°$ = 2.18 kcal/mol. This value differs appreciably from the 2.57 kcal/mol value derived from the *N-tert*-butyl-3-methyl salt (vide supra); we cannot say whether this is due to an accumulation of errors, to a flaw in the assumption that T_1/C (Scheme V) can be taken from the *N-cis*-3,5-trimethyl compound, or to a buttressing effect of the *N-tert*-butyl substituent. In any case it is clear that $-\Delta G°_{Me\text{-}3}$ in the *N*-methylpiperidinium salt is larger than in the free *N*-methylpiperidine (Table VII) and larger than in methylcyclohexane, presumably due to the following causes: (1) N-H is larger than N:, hence syn-axial interaction in the salt is larger than in the free amine. (2) Solvation of the $^+$N-H moiety has the same result of effectively enlarging $^+$N-H over N:. (3) Solvation plus the relative shortness of the C-N (compared to C-C) bond enhances $-\Delta G°$ in the *N*-methylpiperidinium salt over that in cyclohexane.

For *N*,4-dimethylpiperidinium hydrochloride (Table VIII, entry 3), the equation for an equilibrium scheme analogous to Scheme V is $1/K = C_1/T + C_2/T$ with C_1/T again being taken as 1/30.6 and K = 10.1, whence C_2/T = 0.966 and the

Scheme VII



conformational equilibrium constant and $-\Delta G°$ for Me-4 are 15.0 and 1.61 kcal/mol, respectively, in excellent agreement with the value derived from the *N-tert*-butyl-4-methyl salt (vide supra). The $-\Delta G°$ value for the Me-4 group in the salt is somewhat smaller than that in the free amine (Table VII) and that for methylcyclohexane, presumably because of a slightly different molecular shape.

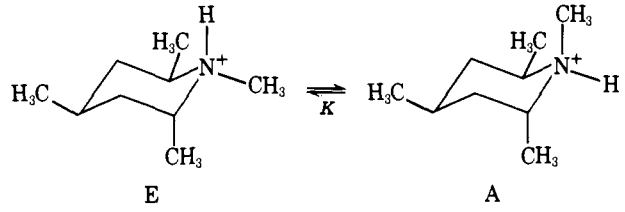
The $-\Delta G°$ values for the *C*-alkyl groups in *N*,*C*-dimethylpiperidinium salts are summarized in Table VII (last line).

The equilibrium schemes for entries 6 and 7, Table VIII, also involve three components each; that for entry 7 is shown in Scheme VI. Here configuration E (characterized by the upfield shifts of C-2 and C-6 caused by the γ_a effect of the axial Me-4) predominates over A; thus $1/K = A_1/E + A_2/E$ or $A_2/E = 1/1.35 - 1/30.6 = 0.71$ and $\Delta G°$ = 0.20 kcal/mol. However, the predominance of E over A_2 is surprisingly small, a difference of 0.6 kcal/mol having been expected according to Table VII. Either the assumption that E/A_1 may be taken from **15m**·HCl (Table VIII, entry 4) is inaccurate or the Me-3e/Me-4a and Me-3a/Me-4e gauche interactions differ by 0.4 kcal/mol; only about half that difference was found in the equilibrium of the corresponding free amines **13mA** = **13mE** (vide supra).

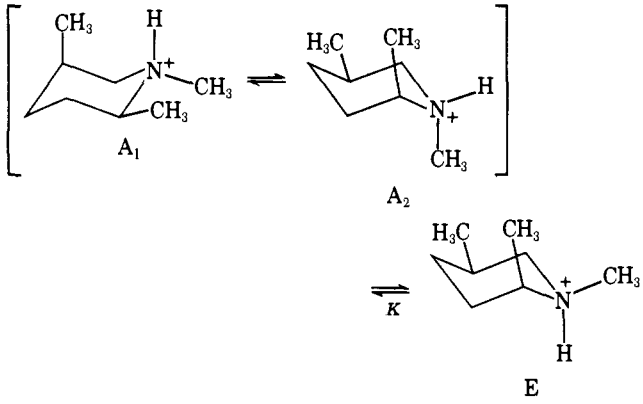
We next take up the more complex four-component equilibrium of **8m**·HCl (entry 9, Table VIII), shown in Scheme VII. By inspecting the scheme we perceive that the E_1 conformation is the preferred one for diastereomer E and A_2 for isomer A, since these are the conformations with single axial methyl groups. This leads to the prediction that C(5) is downfield in the A isomer (β_e effect larger than β_a[23]); hence, from the spectrum (Table IV), the A isomer predominates. Thus $(A_1 + A_2)/(E_1 + E_2)$ = 1.24 (Table VIII). To evaluate individual ratios, two more relationships are required. One of these is A_1/E_1 which may, from the data for the *N*,*cis*-2,4-trimethyl compound (**7m**·HCl Table VIII, entry 5), be set equal to 1/11.2. To evaluate a second relationship, we return to Scheme IV. We noted earlier that, in Scheme IV, T/C_1 = 11.2 and T/C_2 = 11.6; hence $C_1/C_2 = 11.6/11.2 = 1.03$. As a close approximation we may thus assume that the total interactions of N-Me_a,2-Me_e and N-Me_e,2-Me_a are equal. Thus A_1 and A_2 in Scheme VII effectively differ only by the energy of the 4-Me group, which (Table VII) is 1.6 kcal/mol; hence A_2/A_1 = 15.0.

From $(A_1 + A_2)/(E_1 + E_2)$ = 1.24, A_1/E_1 = 1/11.2, and A_2/A_1 = 15.0 one can derive A_2/E_2 = 8.81 and $-\Delta G°$ = 1.3 kcal/mol. The difference between this value and that of an isolated *N*-methyl group (2.1 kcal/mol, Table VIII, entry 4), i.e., 0.8 kcal/mol, may be assumed to represent the 2-Me_a/N-Me_e gauche interaction in conformation A_2 which is absent in E_2. The 2-Me_e/N-Me_a gauche interaction in A_1 has, ac-

Scheme VIII



Scheme IX



cording to the results with **2m**·HCl (Scheme IV, vide supra), the same value, whereas the 2-Me_e/N-Me_e gauche interaction in E_I is formally 0.7 kcal/mol larger, i.e., amounts to 1.5 kcal/mol (by comparison of entries 4 and 5 in Table VIII).[52]

Compound **19m**·HCl (entry 10, Table VIII; Scheme VIII) permits an alternative evaluation of the N-Me_e/2-Me_a interaction. If we compare entry 10 with entry 5, we note that the effect of the axial methyl group at C-6 in **19m**·HCl is to shift the equilibrium (Scheme VIII) to the right by 1.41-0.85 or 0.6 kcal/mol. This must be the value of the N-Me_e/2-Me_a interaction in configuration E which is relieved in configuration A. The agreement with the previously derived value of 0.8 kcal/mol is acceptable, considering the cumulative error of the measurements and calculations.

We finally turn to compound **9m**·HCl (Table VIII, entry 6; Scheme IX) for which $K = E/(A_1 + A_2) = 1.62$. E/A_2 may be set equal to A_2/E_2 in Scheme VII, i.e., 8.81; it then follows that $E/A_1 = 1.99$ and $\Delta G° = -0.41$ kcal/mol. If there were not conformational change at C(5) in the $A_1 \rightarrow E$ interconversion, $\Delta G°$ would be +1.45 kcal/mol (from Scheme IV, T/C_2 and accompanying discussion). The energy gain in shifting Me(5) from the axial (A_1) to the equatorial (E) position is thus 1.86 kcal/mol. This value is unfortunately considerably smaller than the 2.2 kcal/mol derived from **3m**·HCl (Scheme V) and compares even less favorably with the 2.6 kcal/mol value derived from *N-tert*-butyl-3-methylpiperidinium hydrochloride; the very large fluctuations in this value are puzzling. However, even though the 2.2 kcal/mol value lacks the desirable accuracy, it is certain that it exceeds the 1.6 kcal/mol determined for 3-methyl in the *N*-3-dimethylpiperidine free base.

^{13}C NMR Spectra of C-Methylated Piperidines and *N*-Methylpiperidines. The pertinent parameters are summarized in Table III. They should be compared to the corresponding Grant parameters[53] in methylcyclohexanes:[54] α_e 6.0, α_a 1.4, β_e 9.0, β_a 5.4, γ_e −0.3, γ_a −6.3, δ_e −0.6, δ_a 0.2, vic_{cis} −2.9 to −3.4, vic_{trans} −2.5 ppm. In general, the values for piperidines are very similar to those in cyclohexanes; this is true for saturated heterocycles in general.[23] The apparent anomaly in $\alpha_e(2)$ for *N*-methylpiperidine is caused by the fact that this value contains, also, a vic_{trans} component; when one takes this into account, the observed value of 2.4 agrees reasonably with the calculated value (from cyclohexane) of 3.5. On the other hand, the anomaly in $\alpha_a(2)$ appears to be real: whereas this value is positive in cyclohexane, it is negative in piperidine as well as *N*-methylpiperidine;[64] similar negative values are seen in oxanes.[23] The β_e values tend to be low also, though not as low as in other saturated heterocycles.[23] The remaining parameters are unremarkable, except for a large γ_a at C(6) in *N*,2-dimethylpiperidine and a high vic_{cis} value at C(4) in *N*-methylpiperidine. (The vic_{cis} increments at adjacent—i.e., nonsubstituted—positions are normal, being 1.6 in cyclohexane;[53] the corresponding vic_{trans} increments are small, as they are in cyclohexane.)

Experimental Section

The 100-MHz ^1H and 25.16-MHz ^{13}C spectra were measured on a Varian XL-100 pulsed Fourier transform spectrometer in FT mode. Spectra of free amines at room temperature were measured in 5- or 10-mm o.d. tubes in $CDCl_3$ (solvent and lock substance) containing Me_4Si as internal standard and are reported in parts per million from Me_4Si; low-temperature spectra were recorded in either CD_2Cl_2 (NH compounds) or a 1:1 mixture of $CHCl{=}CCl_2$ and CD_3COCD_3 (N-Me compounds) containing Me_4Si in each case. Amine salts were recorded in D_2O (which also served as the lock substance) with 1,4-dioxane, δ = 67.4 ppm,[55] as reference, but shifts are reported from Me_4Si. Analytical gas chromatography was performed with a Hewlett-Packard 5750B instrument equipped with a thermal conductivity detector. The 12 ft × 0.125 in. aluminum column used for analysis of the piperidines was packed with 20% Carbowax 20M plus 10% KOH on Chromosorb W, 80/100 mesh. The column was generally at 75-85 °C, the injection block at 220 °C, and the detector block at 250 °C, and the helium pressure was 50 psi. Preparative separations were carried out on a Varian Aerograph Series 2700 instrument equipped with 0.375-in. columns; the packing and conditions were similar to those used in analysis except that the solid support was Chromosorb A. Hydrogenations were carried out in a Parr low-pressure shaker-type hydrogenation apparatus in 500-mL glass bottles. The catalyst (PtO_2, 83% Pt) was obtained from Engelhard Industries, Inc. Pyridine starting materials were obtained from Aldrich Chemical Co., except for the 3,5-dimethylpyridine, which was from Pfaltz & Bauer, Inc., and were purified prior to hydrogenation by distillation over KOH pellets and sometimes over Raney nickel.

Piperidines. Piperidines and 2- and 4-methylpiperidine were purchased from Aldrich Chemical Co., and *N*-methylpiperidine was purchased from Columbia Organic Chemical Co. All other piperidines were obtained from the corresponding pyridines either by catalytic hydrogenation at 60 psi[56] in concentrated HCl (0.1 mol of pyridine, 50 mL of ice-cold concentrated hydrochloric acid, 12 N, 750 mg of PtO_2, room temperature to 50 °C), or by sodium-absolute ethanol reduction.[57] The latter method was advantageous in some cases when the less stable isomer of a diastereomer pair was desired. Where diastereoisomers were obtained, they were separated by preparative gas chromatography. In general, the e,e isomers emerged before the e,a isomers; identity of products was established by ^1H and ^{13}C NMR spectroscopy; the ^{13}C spectra are recorded in Table I. In the case of 3,5-dimethylpiperidine, separation of the stereoisomers was unsuccessful and the spectrum of the minor isomer in the hydrogenation product mixture (9:1 cis:trans) reported in Table I was obtained from the mixture spectrum. (The major isomer was purified by conversion to the hydrochloride salt and recrystallization followed by treatment with aqueous KOH to recover the free amine.)

***N*-Methylpiperidines.** Methylation was effected by the standard Clarke-Eschweiler procedure.[58] In general, products were purified by preparative gas chromatography; in some instances (notably that of the 3,5 isomer, vide supra) it was found convenient to methylate a cis-trans mixture of piperidines and separate the *N*-methyl derivatives. ^{13}C spectra of the *N*-methylpiperidines are shown in Table II.

***N*,2,4,6-Tetramethylpiperidines.**[59] The product of the sodium-ethanol reduction of 2,4,6-trimethylpyridine (79% yield) was shown, by gas chromatography, to contain five components two of which appeared to be 2,4,6-trimethyltetrahydropyridines. Therefore 12.6 g (0.1 mol) of the product in 150 mL of glacial acetic acid was further hydrogenated at 60 psi hydrogen pressure in a Parr shaker in the presence of 2 g of 10% platinum on charcoal. The usual workup yielded 10.8 g (86%) of a 2,4,6-trimethylpiperidine mixture shown, by a combination of gas chromatography and NMR analysis of the *N*-

methyl derivatives (see below), to consist of 57.3% of the *r*-2,*c*-4,*c*-6 isomer, 15.3% of the *r*-2,*t*-4,*c*-6 isomer, and 27.5% of the *r*-2,*c*-4,*t*-6 isomer.[59]

Methylation of the mixture as described above gave the *N*,2,4,6-tetramethylpiperidines in 92% yield.

***N*-*tert*-Butyl-4-methylpiperidine.** 3-Methyl-1,5-dibromopentane was synthesized by the von Braun procedure as previously described for 1,5-dibromopentane,[60] starting from 4-methylpiperidine. *N*-Benzoyl-4-methylpiperidine (75% yield) melted at 85–87 °C (lit.[61] 83.5–84 °C); 3-methyl-1,4-dibromopentane boiled at 92–95 °C (5 mmHg) (lit.[62] 97–98.5 °C (10 mmHg)), yield 66%.

To 10.83 g (44.4 mmol) of 3-methyl-1,5-dibromopentane in 45 mL of ethanol (95%) was added a solution of 10 g (134 mmol) of *tert*-butylamine in ethanol dropwise over 1 h. The solution was boiled at reflux for 2 days (disappearance of dibromide was checked by GLC analysis of an aliquot). Sodium hydroxide pellets were then added to the cooled solution and most of the ethanol was distilled; further distillation of the residue yielded 4.0 g (58%) of 1-*tert*-butyl-4-methylpiperidine. bp 165–167 °C. IR: 2950 (vs), 2808 (s), 2760 (m), 2715 (w), 2682 (w), 1459 (m), 1400 (m), 1367 (s), 1347 (w), 1280 (s), 1211 (s), 1158 (m), 1129 (m), 1072 (m), 967 (m), 951 (m), 817 (m), 740 (s) cm^{-1}. ^1H NMR: δ 0.8–1.0 (ca. d, J = 2 Hz, 3 H), 1.05 (s, 9 H), 1.2–1.7 (m, 5 H), 2.0 (t, J = 11 Hz, 2 H), 2.9 ppm (d, J = 11 Hz, 2 H). ^{13}C NMR: 21.90 (CH_3C), 26.18 (Me_3C), 31.20 (C-4), 35.35 (C-3,5), 46.25 (C-2,6), 53.71 ppm (Me_3C).

Anal. Calcd for $C_{10}H_{21}N$: C, 77.35; H, 13.63. Found: C, 77.29; H, 13.43.

Picrate: mp 172–174 °C.

***N*-*tert*-Butyl-3-methylpiperidine.** This compound was synthesized in exactly analogous fashion starting from 3-methylpiperidine. *N*-Benzoyl-3-methylpiperidine was obtained in 86% yield and converted to 2-methyl-1,5-dibromopentane, bp 103–105 °C (10 mmHg) (Kugelrohr) (lit.[63] 98–99 °C (11 mmHg)), in 47% yield. *N*-*tert*-Butyl-3-methylpiperidine, bp 80–82 °C (60 mmHg) (Kugelrohr), was obtained in 61% yield. ^1H NMR: δ 0.81 (d, J = 6 Hz, 3 H + 1 H), 1.04 (s, 9 H), 1.60 (broad m, 5 H), 2.92 (broad m, 2 H) ppm. ^{13}C NMR: δ 19.80 (Me), 25.73 (Me_3C), 26.15 (C-5), 31.55 (C-3), 33.16 (C-4), 45.93 (C-6), 53.40 (Me_3C), 54.24 (C-2).

Parametrization of NMR Spectra (Tables I–III). The treatment of the chemical shifts by multiple linear regression analysis was effected as previously described.[28]

Low-Temperature Equilibria. Pertinent low-temperature chemical shift data for **5** (−90 °C), **8** (−95 °C), **9** (−80 °C), **13** (−90 °C), and **3m** (−100 °C) as well as **5m**, **8m**, **9m**, and **13m** (all at −80 °C) in $CD_3COCD_3/CHCl{=}CH_2$ are shown in Table V. The italicized peaks are the ones which were integrated (see below). The standard deviations from integration of different peaks and by different methods (electronic integration or planimeter) were 1% or less. In the case of **3m** the integration was done visually by counting square millimeters under the peaks on the coordinate paper as well as by the other two methods. The percentage of the minor isomer ranged from 0.8 to 1.4; the corresponding range in $-\Delta G°$ is 1.46–1.66 kcal/mol.

Room-temperature and low-temperature spectra in $CD_3COCD_3/CHCl{=}CCl_2$ were also recorded for the conformationally homogeneous compounds **2m**, **4m**, **7m**, **10m**, **11m**, **14m**, and **15m** and the conformationally degenerate compounds **12**, **12m**, and **16m.** In the case of the conformationally locked compounds, small shift changes (usually not exceeding 0.5 ppm and almost invariably downfield) were caused by the change of the solvent from $CDCl_3$ to $CD_3COCD_3/CHCl{=}CCl_2$; further changes of about the same magnitude but upfield (except for the *C*-methyl groups) were caused by change of the temperature from ambient to −80 °C. In the case of the degenerate compounds, decoalescence of C(2,6), C(3,5), and the *C*-methyl groups occurred at low temperature as follows: **12**, C(2) (axial Me substituent) 47.52, C(3), 30.40, C(4), 19.77, C(5), 35.07, C(6), 44.27, Me(2), 18.13, Me(6), 23.62. **12m**, C(2), 55.66, C(3), 32.04, C(4), 19.44, C(5), 35.24, C(6), 50.47, Me(2), 8.59, Me(6), 21.38, N-Me, 40.17. **15m**, C(2), 61.27, C(3) (axial Me substituent), 29.02, C(4), 38.45, C(5), 25.91, C(6), 64.71, Me(3), 18.82, Me(5), 20.17, N-Me, 46.93.

NMR Spectra and Conformational Analysis of *N*-Methylpiperidine Hydrochlorides. To a 2 N solution of HCl in D_2O was added dropwise, from a syringe, the appropriate amine purified by preparative GLC. The pH was followed on an Orion Research Model 701 digital pH meter and the progress of the titration was also monitored by ^1H NMR with a Hitachi Perkin-Elmer R-24B 60-MHz NMR spectrometer. Addition of the amine was stopped when the N-CH_3 signals of the equatorial and axial *N*-methyl groups in the salts coalesced, usually at a pH of about 8. More 2 N HCl/D_2O was then added in small drops so as to lower the pH 2–3 units. The solution was then transferred to a 5- or 10-mm NMR tube and the ^{13}C spectrum was recorded on the Varian XL-100 instrument. The pertient spectra are listed in Table IV; in all cases (save that of *N*-methylpiperidinium hydrochloride, which is subject to rapid ring reversal which interconverts the two isomers) the spectra of both isomers were seen. Several pairs of well-separated peaks (italicized in Table IV) were then integrated by expansion and electronic integration (integrator trace) as well as, in some cases, area measurement by means of a Keuffel & Esser compensating Polar Planimeter Model 4242. Consistent integrations (within ±2%) were obtained from different pairs of peaks and by the two different techniques. The equilibrium constants and corresponding $-\Delta G°$ values are listed in Table VIII.

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Influence of Substituents at the 5 Position on the Structure of Uridine

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Abstract: The conformations of 5-substituted uridines, some of which are found in the first anticodon position of tRNAs, have been studied by X-ray crystallography, ^1H NMR spectroscopy, and quantum-chemical methods. The results clearly demonstrate that the electronic effect of a substituent X at the 5 position influences not only the base moiety, but also (1) the N(1)–C(1′) and C(1′)–O(1′) bonds in opposite ways and (2) the conformation of the ribose via the dihedral angle χ about the glycosidic bond. This can be rationalized in simple MO schemes using the concepts of "through-bond" and "through-space" interaction which result in an electron transfer from O(1′) to X. EH and MINDO/3 calculations suggest that the ribosyl moiety acts as a variable donor whose strength depends on χ and X. The favored χ values of C(2′)-*endo*- and C(3′)-*endo*-uridine predicted by MINDO/3 are in line with the experimental data.

Introduction

In addition to the four standard bases A, U, C, and G there are a remarkable number of modified nucleosides present in tRNAs.[1] 5-Substituted uridines (x^5U) and 2-thiouridines (s^2x^5U) occur in the first anticodon ("wobble")[2] position (Figure 1), where uridine itself is only found exceptionally. Although 5 substituents do not directly participate in the formation of hydrogen bonds, they strongly influence the codon recognition of urdine and effect a significant modulation of the base pairing between mRNA and tRNA.[3] The three-dimensional structure of yeast $tRNA^{Phe}$ [4,5] shows the "wobble" nucleoside in a sterically exposed position being the terminator of the anticodon helix.[6] The codon–anticodon interaction is likely to be influenced by the conformations of the two trinucleoside diphosphates involved. Substituents at the "wobble" base could modify the exact conformation and hence the base-pairing properties of the anticodon. We have studied the influence of substituents at the 5 position on the structure of uridine with the aid of X-ray crystallography, ^1H NMR spectroscopy, and quantum-chemical calculations.

Results and Discussion

A. Hypotheses Arising from Crystal Data. The replacement of the hydrogen atom at the 5 position of uridine by a substituent with different electronic properties will change the electron distribution within the π system and hence the geometry of the heterocyclic base, especially if the 5 substituent has not only an inductive but also a mesomeric effect. π-Accepting and π-donating substituents have opposing effects on bond lengths which can be predicted by a simple scheme (Figure 2). This agrees well with the bond lengths observed in crystal structures.[7]

A detailed analysis of published strcutres indicates that 5 substituents influence not only the π system, but also the glycosidic bond N(1)–C(1′) and, to a lesser degree, C(1′)–O(1′). These bonds change gradually going from 5-nitrouridine to 5-aminouridine (Table I[8–14]). Electron-withdrawing 5 substituents lead to a lengthening and electron-donating groups to a shortening of the N(1)–C(1′) bond with reverse effect on

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