Steric Effects on the Configuration at Nitrogen in Piperidines

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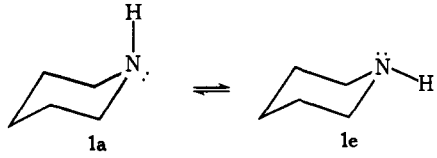
Abstract: The proportion of the N proton in piperidine that exists in the axial position is reduced by introduction of a 3-axial methyl group. The axial–equatorial chemical-shift differences between the α protons in 3,3-dimethylpiperidine and its *N*-methyl derivative are increased over the values in the compounds lacking the *gem*-dimethyl grouping. These increases are nullified by protonation at nitrogen. This evidence indicates that the large amount of NH axial in piperidine is due to attractive syn-axial H–H interactions. The barriers to ring reversal in 3,3-dimethylpiperidine, 1,3,3-trimethylpiperidine, and 1,4,4-trimethylpiperidine are reported.

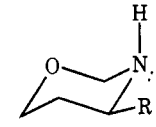
Conformational analysis has traditionally been dominated by considerations of repulsive nonbonded interactions. The preference of anti over gauche *n*-butane and of equatorial over axial methylcyclohexane has been conveniently discussed in terms of repulsive steric effects. The term "steric effect" in fact has come almost to denote the increase or decrease of a repulsive interaction in either ground states (equilibrium constant effect) or transition states (rate constant effect). Only recently has it been fully appreciated that attractive nonbonded interactions (aside from dipole–dipole effects) can have an important influence on rates and equilibrium constants. In the conformational analysis of organosilicon compounds and other materials with atoms from beyond the first row, the longer bond lengths can make interactions more attractive than in the analogous hydrocarbons.[2] Even in the hydrocarbon cyclohexane, calculations have repeatedly shown that an axial hydrogen experiences attractive interactions with the other syn-axial hydrogens.[3] Larger substituents suffer respulsive interactions and prefer the equatorial position, but the favorable attractive interactions give a proton an inherent preference for the axial position.

The piperidine system (eq 1) possesses a single proton



1a ⇌ **1e** (1)

on nitrogen and no second substituent,[4] so the expected preferred conformation should be NH axial (**1a**). This conclusion has been explicitly tested on the piperidine system by conformational calculations,[5] and the axial form was found to be favored by 0.6 kcal/mol. The conformational preference of the proton on nitrogen in piperidine has vexed the field of conformational analysis for some 15 years,[6] without as yet reaching a consensus.[7] There has been no direct measure of the axial–equatorial equilibrium constant, coupled with an unambiguous assignment of conformer identity. Three nmr methods have given evidence that the N proton qualitatively prefers the axial orientation. (1) An axial N proton gives an unambiguously large vicinal coupling constant with the adjacent axial protons. Booth and Lemieux[8] were thus able to prove that tetrahydro-1,3-oxazine and its 4-methyl derivative prefer the axial conformer (**2**, **3**).



2, R = H
3, R = CH_3

Unfortunately, this method failed[8,9] for piperidine itself, presumably because of proton exchange. (2) The α protons and the ^{13}C nuclei give different pseudocontact paramagnetic shifts when the substituent on nitrogen is axial from when it is equatorial.[10] By this method, 3- and 4-methylpiperidine and piperidine itself were found to have the NH axial, but 1-methyl- and 1,4-dimethylpiperidine have the NCH_3 equatorial.[10] (3) The chemical-shift difference between the diastereotopic protons α to the heteroatom has been found to be sensitive to nitrogen configuration.[11] Although for an NH-

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(2) (a) Organosilicon examples: R. J. Ouellette and S. H. Williams, *J. Amer. Chem. Soc.*, **93**, 466 (1971); (b) organophosphorus examples: J. B. Lambert, W. L. Oliver, Jr., and G. F. Jackson, III, *Tetrahedron Lett.*, 2027 (1969); (c) J. B. Lambert and W. L. Oliver, Jr., *Tetrahedron*, **27**, 4245 (1971); (d) organosulfur examples: J. B. Lambert, R. G. Keske, and D. K. Weary, *J. Amer. Chem. Soc.*, **89**, 5921 (1967); (e) J. B. Lambert, D. S. Bailey, and C. E. Mixan, *J. Org. Chem.*, **37**, 377 (1972).

(3) J. B. Hendrickson, *J. Amer. Chem. Soc.*, **83**, 4537 (1961); D. S. Bailey, J. A. Walder, and J. B. Lambert, *ibid.*, **94**, 177 (1972); M. Bixon and S. Lifson, *Tetrahedron*, **23**, 769 (1967).

(4) The lone pair is best treated not as a "substituent" with steric boundaries but as part of the entire electronic structure of the molecule: S. Wolfe, A. Rauk, L. M. Tel, and I. G. Csizmadia, *J. Chem. Soc. B*, 136 (1971). Its placement (axial or equatorial), however, may still be discussed.

(5) N. L. Allinger, J. A. Hirsch, and M. A. Miller, *Tetrahedron Lett.*, 3729 (1967); also see N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *J. Amer. Chem. Soc.*, **91**, 337 (1969), for analogous calculations and conclusions in sulfur systems.

(6) D. H. R. Barton and R. C. Cookson, *Quart. Rev., Chem. Soc.*, 10, 44 (1956).

(7) A listing of references may be found in ref 2c according to the schools that favor (a) NH axial, (b) NH equatorial, and (c) equal proportions.

(8) H. Booth and R. U. Lemieux, *Can. J. Chem.*, **49**, 777 (1971).

(9) J. B. Lambert and R. G. Keske, unpublished results.

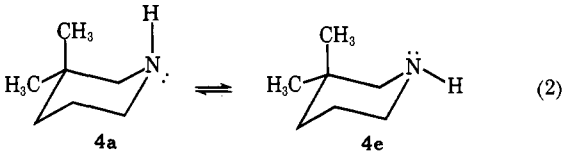
(10) T. Yonezawa, I. Morishima, and Y. Ohmori, *J. Amer. Chem. Soc.*, **92**, 1267 (1970); I. Morishima, K. Okada, T. Yonezawa, and K. Goto, *ibid.*, **93**, 3922 (1971).

(11) (a) H. P. Hamlow, S. Okuda, and N. Nakagawa, *Tetrahedron Lett.*, 2553 (1964); (b) F. Bohlmann, D. Schumann, and H. Schulz, *ibid.*, 173 (1965); (c) F. Bohlmann, D. Schumann, and C. Arndt, *ibid.*, 2705 (1965); (d) F. G. Riddell, *J. Chem. Soc. B*, 560 (1967); (e) J. B. Lambert and R. G. Keske, *J. Amer. Chem. Soc.*, 88, 620 (1966); (f) J. B.

axial conformer, δ_{ae} (α) is close to the normal cyclohexane value (0.4–0.5 ppm), an enhanced value is found in the equatorial isomer (0.8–1.0 ppm), attributed to an $n \rightarrow \sigma^*$ interaction[11a] between the axial lone pair and the anti-periplanar α-axial hydrogens. Only the α-axial hydrogens are shifted upfield by the axial lone pair; the equatorial protons remain unshifted.[11e] By this method, piperidine was shown to be predominately NH axial and *N*-methylpiperidine NCH_3 equatorial.

This last method, based on δ_{ae} (α), is the subject of the present study. It was pointed out[12] that the enhanced value of δ_{ae} (α) in *N*-methylpiperidine could be due either to an effect of the axial lone pair or of the equatorial methyl group. Although the comment was legitimate, the average lone-pair effect (30 Hz) proved to be much larger than the average methyl effect (10 Hz), so the original conclusions of the method remained valid.[13] Nonetheless, an enhanced δ_{ae} (α) had never been measured in the absence of an N-alkyl substituent, possibly because all systems without such a substituent possess an axial N proton. We therefore set about to design a system in which an enhanced δ_{ae} (α) could be observed without an alkyl substituent on nitrogen. Such an observation would confirm the conclusions previously based on the magnitude of δ_{ae} (α).

The system chosen to attain our goals was 3,3-dimethylpiperidine (**4**). This molecule permits the study of the interaction of an axial methyl group with the hydrogen or lone pair in the 1-axial position (eq 2). If



(2)

the 1,3-syn-axial CH–NH interactions in piperidine (**1**) are attractive, introduction of the axial methyl group (**4**) would increase the proportion of NH equatorial by increasing the repulsive interactions in the NH-axial isomer. On the other hand, if the lone pair in piperidine is "larger" in the traditional sense,[4] the increased 1,3-syn-axial lone-pair–hydrogen interactions would drive the equilibrium toward an even greater proportion of NH axial.

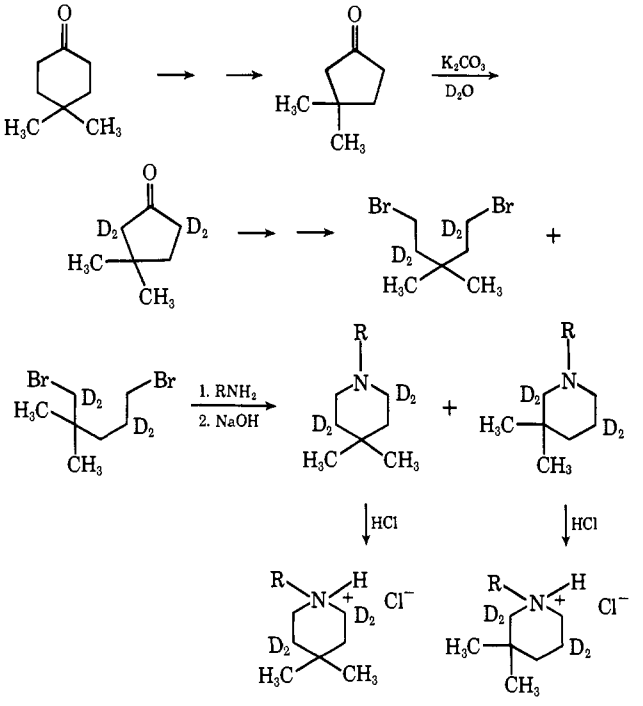
The experiment as described constitutes not only a test of the explanation for the large amount of NH axial in piperidine and analogous systems[2b–e] (attractive H–H interactions rather than repulsive H–lone-pair interactions), but also a test of the nmr method of analysis for these systems.[11] If the introduction of the 3-axial methyl group shifts the equilibrium from **4a** to **4e** (eq 2), δ_{ae} (α) should increase. If enhanced values of δ_{ae} (α) were caused only by the anisotropy of an adjacent N-alkyl group[12] on the other hand, then a shift in equilibrium would have no effect on δ_{ae} (α). An enhanced value of δ_{ae} (α) for **4** over **1** would therefore constitute simultaneous proof that δ_{ae} (α) is primarily sensitive to lone-pair orientation and that the determining factor in the NH-axial preference in piperidine is an attractive axial–axial interaction.[14]

Results

The method under consideration requires the observation of the chemical-shift difference between the protons α to nitrogen in 3,3-dimethylpiperidine (**4**). For the 2α protons, δ_{ae} (α) is severely perturbed by the adjacent methyl groups. For the 6α protons, however, the methyl groups four carbons removed have no effect on δ_{ae} (α).[15] Since the only desired quantity is therefore δ_{ae} (6), the 2 protons must be removed by replacement with deuterium. Furthermore, in order to analyze the 6α resonances, the coupling to the 5β protons must be suppressed by deuteration at that position. The desired molecule is therefore 3,3-dimethylpiperidine-*2,2,5,5-d*$_4$. We also examine δ_{ae} (6) in 1,3,3-trimethylpiperidine-*2,2,5,5-d*$_4$ (**5**) to contrast the properties of the NH and NCH_3 series. The protonated forms of both these molecules are necessary models, because protonation should remove any direct effect of the lone pair and return δ_{ae} (6) to its normal value. Any enhancement in δ_{ae} (6) that is not removed by protonation must be due to an effect from the N substituent rather than the lone pair.

The synthesis of the desired compounds (**4**-*d*$_4$, **5**-*d*$_4$, **4**H$^+$-*d*$_4$, and **5**H$^+$-*d*$_4$) is given in Scheme I. The preparation of the dibromides has been discussed elsewhere,[2e] but the experimental procedures are given here. 4,4-Dimethylpiperidine-*2,2,5,5-d*$_4$ (**6**) and 1,4,4-trimethylpiperidine-*2,2,5,5-d*$_4$ (**7**) are major by-products of the synthesis. Separation of the 3,3 and 4,4 isomers was achieved by preparative gas chromatography. Identical nmr experiments have been carried out for both series, but the results from the 4,4 compounds are not central to this discussion since it is known that a 4-axial

Scheme I



Lambert, R. G. Keske, R. E. Carhart, and A. P. Jovanovich, *ibid.*, **89**, 3761 (1967); (g) W. J. Kasowski and J. C. Bailar, Jr., *ibid.*, **91**, 3212 (1969); (h) P. J. Chivers, T. A. Crabb, and R. O. Williams, *Tetrahedron*, **24**, 6625 (1968), and preceding papers in this series; (i) F. G. Riddell and J. M. Lehn, *J. Chem. Soc. B*, 1224 (1968); (j) P. J. Halls, R. A. Y. Jones, A. R. Katritzky, M. Snarey, and D. L. Trepanier, *ibid.*, 1320 (1971).

(12) M. J. T. Robinson, *Tetrahedron Lett.*, 1153 (1968); H. Booth and J. H. Little, *Tetrahedron*, **23**, 291 (1967).

(13) J. B. Lambert and R. G. Keske, *Tetrahedron Lett.*, 2023 (1969).

(14) J. B. Lambert, D. S. Bailey, and B. F. Michel, *ibid.*, 691 (1970).

(15) H. Booth, *Tetrahedron*, **22**, 615 (1966).

methyl group strongly perturbs δ_{ae} (α) by deshielding the syn-axial α protons.[15] Such an effect is not present in the 3,3 series. The nmr spectra were taken at −80° on 15% solutions at 60 or 90 MHz. The chemical-shift differences and coupling constants are reported in Table I. In order to determine δ_{ae} (6), spectra were observed at the slow exchange limit below the coalescence temperature for ring reversal.[11e,f] Data for the parent piperidine-*3,3,5,5-d*$_4$ (**1**) and *N*-methylpiperidine-*3,3,-5,5-d*$_4$ (**8**) are included in Table I for comparison.[11f]

Table I. Spectral Parameters for Piperidines (−80°)

Compd	Solvent	δ_{ae} (6), ppm	J_{ae} (6), Hz
4	CD_3OD	0.61[a,b]	13.0
	CH_2Cl_2	0.66[a]	13.5
5	CD_3OD	1.11[a]	11.7
	CH_2Cl_2	1.20[a]	11.5
	Toluene-d_8	1.19[a]	11.7
6	Freon 22	0.10[b]	~12
7	CD_3OD	0.50[a]	12.4
	CH_2Cl_2	0.58[a]	12.0
1[c]	CD_3OD	0.44[a]	11.9
	CH_2Cl_2	0.48[a]	12.3
	Toluene-d_8	0.54[a]	11.2
8[c]	CD_3OD	0.94[a]	11.4
	CH_2Cl_2	1.02[a]	11.2
	Toluene-d_8	1.10[a]	11.0
4H$^+$Cl$^-$	CD_3OD	0.43[a,b]	12.0
5H$^+$Cl$^-$	CD_3OD	0.47[a,b]	12.6
6H$^+$Cl$^-$	CD_3OD	<0.1[b]	
7H$^+$Cl$^-$	CD_3OD	0.14[a,b]	12.5
1H$^+$Cl$^-$[c]	CD_3OD	0.40[a]	13.1
8H$^+$Cl$^-$[c]	CD_3OD	0.44[a]	12.0

[a] Measured at 60 MHz. [b] Measured at 90 MHz. [c] Data from ref 11f.

Kinetic studies of the ring-reversal process have also been carried out for **4**, **5**, and **7** by standard complete line-shape methods.[11f] The activation parameters are given in Table II. The introduction of the *gem*-dimethyl grouping lowers the barrier slightly in comparison to the barriers for **1** and **8**.[11f] The small value of δ_{ae} (6) precluded analogous measurements on **6**.

Table II. Activation Parameters to Ring Reversal in *gem*-Dimethylpiperidines in CD_3OD

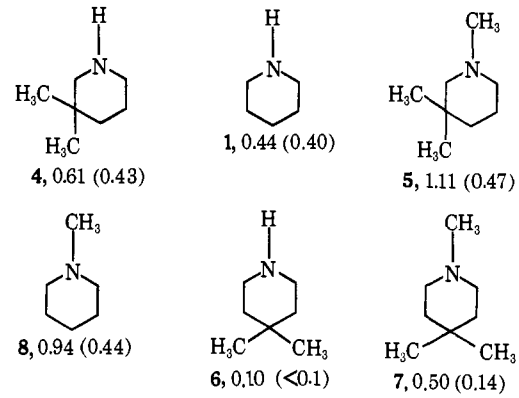
	4[a]	**5**[b]	**7**[a]
E_a, kcal/mol	12.3	10.8	11.2
Log A	14.4	11.7	12.1
$\Delta H^{\ddagger}$, kcal/mol	11.7	10.3	10.6
$\Delta S^{\ddagger}$, kcal/mol	5.6	−6.9	−5.0
Corr coeff	0.994	0.997	0.996
No. of pts	10	12	9

[a] Analysis of the A_2-to-AB change in the C-6 resonance. [b] Analysis of the one-peak to two-peak change in the methyl resonance.

Discussion

The data for the molecules under study are summarized in Chart I. The values of δ_{ae} (6) in ppm for the free bases in CD_3OD are given, followed parenthetically by the values of δ_{ae} (6) for the protonated forms in the same solvent. Three comparisons need to be made: (1) each NH compound with the corresponding NCH_3 compound; (2) each unmethylated (on carbon) compound with the corresponding 3,3-dimethyl compound;

Chart I



and (3) each free base with its protonated form. For piperidine (**1**), δ_{ae} (6) is very close to the value for cyclohexane, so the N proton must be predominantly axial and the lone pair equatorial. For *N*-methylpiperidine (**8**), δ_{ae} (6) is considerably enhanced, so the *N*-methyl group is predominantly equatorial and the lone pair axial.[11e,f] On protonation, δ_{ae} (6) for the *N*-methyl compound is leveled to that of the free NH compound, for which δ_{ae} (6) on protonation remains almost unchanged (within 0.04 ppm). Thus there seems to be little direct effect of the *N*-methyl group on δ_{ae} (6).[16] These conclusions based on δ_{ae} (6)[11e,f] are in good agreement with the calculations of Allinger, *et al.*[5] (NH axial by 0.6 kcal/mol; NCH_3 equatorial by 0.8 kcal/mol).

Introduction of the 3,3-dimethyl grouping increases δ_{ae} (6) in the NH compound by 0.17 ppm and in the NCH_3 compound by a like amount. In both cases the population of the equatorial isomer must therefore have increased, although the proportionate change is much larger for NH than for NCH_3. Because a syn-axial CH_3–CH_3 interaction is extremely large, the methyl group in **5** must be entirely equatorial, and the 1.11-ppm value for δ_{ae} (6) can be taken as a model for this conformational extreme. The N proton in **4** is therefore by no means all equatorial, and a quantitative analysis would show that it is probably still on the axial side of the equilibrium, in agreement with the calculations[5] (NH axial by 0.1 kcal/mol).[17]

The data from the protonated species are in accord with these conclusions. In contrast to protonation of piperidine (no change), protonation of 3,3-dimethylpiperidine (**4**) decreases δ_{ae} (6) by 0.18 ppm, to a value (0.43 ppm) nearly identical with those of piperidine (0.44) and protonated piperidine (0.40). Protonation removes the shielding effect of the axial lone pair. Similarly, protonation of 1,3,3-trimethylpiperidine (**5**) decreases δ_{ae} (α) by 0.64 ppm to 0.47, close to the values for protonated *N*-methylpiperidine (0.44) and all the protonated NH compounds, as well as free piperidine. Again the effect of the lone pair has been removed, and there is little or no residual *N*-methyl effect. The nearly identical values of δ_{ae} (6) for protonated **1**, **4**, **5**, and **8** confirm the use of enhancements in δ_{ae} (6) to detect contributions from an axial lone-pair species.

(16) In methylcyclohexane, there is a larger methyl effect of about 0.25 ppm, but the ring shape is different; *cf.* J. B. Lambert and Y. Takeuchi, *Org. Magn. Resonance*, 1, 345 (1969).

(17) In the analogous sulfur system, the introduction of a 3,3-dimethyl grouping does not alter the strong axial preference (>1.5 kcal mol) of the S proton (ref 2e). The longer C–S bonds enable even the syn-axial CH_3–H interaction to remain attractive.

The reduction in the proportion of NH axial by introduction of a 3-axial methyl group indicates that the original preference was most likely due to attractive syn-axial H–H interactions. If the preference had been because the lone pair was "sterically larger,"[4] then the 3-axial methyl should have increased the NH-axial (lone-pair–equatorial) form. There is a small but real solvent dependence of δ_{ae} (6) in the free bases (Table I), larger values being observed in toluene or methylene chloride than in methanol. Since almost uniform changes are observed for all the molecules (about 0.07 ppm between methanol and toluene), the different values are more likely inherent characteristics of each solvent (ASIS for toluene) than responses to changes in the axial–equatorial equilibrium constant. Solvent effects on the equilibrium are expected to be small if the intramolecular nonbonded interactions are the primary conformational determinant.

A 4-axial methyl group deshields the syn-axial 2,6 protons without significantly affecting the equatorial protons,[15] so δ_{ae} (6) in the 4,4-dimethylpiperidines should be lower than in the 3,3-dimethyl and unmethylated compounds. Direct comparisons of δ_{ae} (6) between the two series cannot therefore be made. For 1,4,4-trimethylpiperidine (**7**), δ_{ae} (6) is 0.50 ppm; on protonation it becomes 0.14. The protonated value is very close to that of unprotonated or protonated 4,4-dimethylpiperidine (0.10), so a parallel analysis of the 4,4 series can be made with all values of δ_{ae} (6) reduced by 0.30–0.35 ppm. 4,4-Dimethylpiperidine is primarily NH axial with a δ_{ae} (6) of 0.10, and 1,4,4-trimethylpiperidine primarily NCH_3 equatorial with an enhanced δ_{ae} (6) of 0.50. This enhanced value is reduced to the normal value (for this series) on protonation.

Summary. Introduction of a 3-axial methyl group increases δ_{ae} (6) in piperidine and *N*-methylpiperidine by about 0.17 ppm. On protonation, δ_{ae} (6) for both compounds (**4**, **5**) reverts to a value close to those of protonated or unprotonated piperidine (**1**) and protonated *N*-methylpiperidine (**8**). Deviations of δ_{ae} (6) from this leveled value in the free bases are therefore a direct measure of contributions from the NR-equatorial (lone-pair axial) conformer: **1** < **4** < **8** < **5**. The decrease in NH axial for 3,3-dimethylpiperidine (**4**) shows that the original preference is due to attractive syn-axial H–H interactions.[18] The enhanced value of δ_{ae} (6) for **4** is the first such observation in the absence of an N-alkyl group. This enhancement, and its reversion to a normal value on protonation, proves that δ_{ae} (6) is a valid indicator of the location of the lone pair on nitrogen.[11]

It should be noted that a compound with an axial alkyl group in the 1, 2, 4, or 5 positions gives perturbed (smaller) values[15] of δ_{ae} (6) that cannot be compared directly to the values in the unsubstituted or 3-substituted series. Thus, any compound with an axial 1-alkyl substituent, for example, cannot be used as the model for the lone-pair equatorial isomer. Failure to recognize this problem has produced several incorrect applications of the δ_{ae} (α) method.[11i,11j,19] In any of these perturbed cases, valid conclusions may be reached if the magnitude of δ_{ae} (α) for the free base is compared with that of its protonated analog. It is this shift that is the best indicator of an axial pair, rather than the absolute magnitude of δ_{ae} (α).

(18) An interpretation of the conformational preference entirely in terms of the syn-axial interaction is a considerable oversimplification of a complicated situation. Although this interaction may be dominant, other H–H and H–C interactions, as well as angle deformations, certainly contribute to the final conformational results.

(19) R. F. Farmer and J. Hamer, *Tetrahedron*, **24**, 829 (1968).

Experimental Section

Infrared spectra were recorded on Beckman IR-5 and IR-10 spectrometers. Nmr spectra were measured on Varian A-60 and T-60 spectrometers at 60 MHz and on the Bruker HFX-10 spectrometer at 90 MHz.[20] Computer analyses were performed on a CDC-6400 with Calcomp plotting accessories. Vapor-phase chromatography was carried out on Hewlett–Packard Model 700 and Varian Aerograph Model 1520b instruments.

4,4-Dimethylcyclohex-2-enone was prepared in 36% yield by condensation of isobutyraldehyde and methyl vinyl ketone following the procedure of Bordwell and Wellman.[21]

4,4-Dimethylcyclohexanone was prepared by hydrogenation of the above compound in acetic acid; sublimed sample mp 39–40° (lit.[21] 39–40°).

3,3-Dimethyladipic acid was prepared in 55% yield by potassium permanganate oxidation of the above ketone.

3,3-Dimethylcyclopentanone. 3,3-Dimethyladipic acid (20 g) was heated to 320° with 5 g of anhydrous $Ba(OH)_2$ in a flask equipped with a short-path distillation head. The crude product was distilled from the reaction mixture. Duplicate runs were combined and redistilled to give an overall 29% yield of the desired product. Alternatively, the diacid was converted to the diester, cyclized with NaH, and decarboxylated to the ketone.

3,3-Dimethylcyclopentanone-*2,2,5,5-d*$_4$ was obtained by K_2CO_3-catalyzed exchange with seven successive portions of fresh D_2O. The deuterium incorporation, determined by nmr integration of the ring protons, was 99.5% at the α positions.

2,2- and 3,3-Dimethyl-1,5-pentanediol-*1,1,4,4-d*$_4$. This mixture was prepared by a Baeyer–Villiger oxidation of the above deuterated ketone,[22] followed by a lithium aluminum hydride reduction. To 7.0 ml of H_2O_2 in 60 ml of CH_2Cl_2 in a 250-ml, round-bottomed flask cooled to 0° was added 55 g of trifluoroacetic acid with stirring. To this mixture, 11 g of cyclopentanone-*2,2,5,5-d*$_4$ in 20 ml of CH_2Cl_2 was added over a 90-min period with the temperature below 10°. The mixture was taken up in 100 ml of CH_2Cl_2, extracted with H_2O and 5% Na_2CO_3, dried over $MgSO_4$, and evaporated. The oil (lactone) was taken up in 70 ml of ether and added dropwise to 5 g of $LiAlH_4$ in 200 ml of ether. The solution was hydrolyzed with 24 g of 5% NaOH. The precipitate was filtered, washed with ether, and twice extracted with boiling tetrahydrofuran. The organics were concentrated and combined with the products of several parallel preparations to give 19 g (81%) of the diol mixture. By vpc comparison with synthetic mixtures of authentic diols (below), the deuterated mixture was found to be 60:40 favoring the 2,2-dimethyl compound.

2,2- and 3,3-Dimethyldibromopentane-*1,1,4,4-d*$_4$. The method of Wiley[23] was utilized in order to avoid methyl migration. In a 250-ml, three-necked flask equipped with a magnetic stirrer were placed 4.9 g of the diol, 20.5 g of triphenylphosphine, and 80 ml of distilled dimethylformamide. To this mixture, 12.1 g of bromine was added until a faint yellow color persisted. The DMF was removed by distillation and the dibromide mixture was collected at 80° (1.6 mm) along with a small amount of triphenylphosphine oxide. The mixture was treated with water, taken up in ether, dried, and evaporated to give 4.1 g (42%) of the pure dibromides, identical with authentically prepared samples (see below).

3,3- and 4,4-Dimethylpiperidine-*2,2,5,5-d*$_4$ (4 and 6) were prepared and purified by the procedure used for the unmethylated material.[11f] The two products were distinguished by comparison of vpc retention times with authentic undeuterated samples (prepared below). The compounds were preparatively separated by vpc using a 15-ft column of 20% Carbowax 20M, 3% tetraethylenepentamine, and 3% KOH on Chromosorb W.[24]

(20) We thank the National Science Foundation for funds that enabled us to purchase signal-averaging equipment for the HFX-10.

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(22) W. D. Emmons, *J. Amer. Chem. Soc.*, **76**, 3468 (1954).

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3,3- and 4,4-Dimethyl-*N*-methylpiperidine-2,2,5,5-d_4 (5 and 7) were prepared as above using a 20% methylamine–methanol solution.[11f] The compounds were identified by comparison of vpc retention times with authentic samples (prepared below). The *N*-methylpiperidines were preparatively separated by vpc as above.

3,3- and 4,4-Dimethylpiperidines. Authentic samples of these compounds and their *N*-methyl analogs were separately prepared by lithium aluminum hydride reduction of commercially available 2,2- and 3,3-dimethylglutaric methyl esters, followed by bromination and cyclization as for the above deuterated compounds. At each step, these materials were used to identify isomers prepared by the above routes.

Nmr Sample Preparations. The piperidines were weighed into an nmr sample tube and the appropriate amount of solvent was added to give a 15% solution (w/v). Protonated piperidines were prepared in CD_3OD by flushing the nmr sample tubes with HCl gas in successive portions until no further shift of the β-methylene protons was observed.

Ring Openings of Trimetaphosphoric Acid and Its Bismethylene Analog. Syntheses of Adenosine 5′-Bis(dihydroxyphosphinylmethyl)phosphinate and 5′-Amino-5′-deoxyadenosine 5′-Triphosphate

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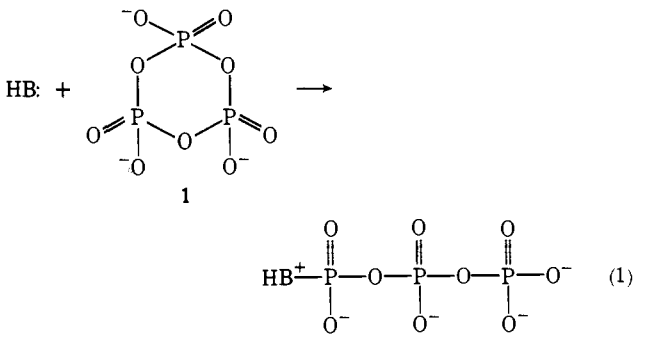
Abstract: The reactions of some alcohols with salts of trimetaphosphoric acid in nonaqueous solutions were investigated. Both the ease of ring opening and product distributions were found to be strongly dependent upon whether the solutions were acidic or basic. With acid catalysis, anhydrous methanol reacted with tricyclohexylammonium trimetaphosphate to give methyl phosphate as the only detectable esterified product, even in the early stages of the reaction; in basic media the products were identified as methyl mono-, di-, and triphosphate and inorganic mono-, di-, and triphosphate. The yield of the simple ring-opening product, methyl triphosphate, never exceeded approximately 10%. When 5′-amino-5′-deoxyadenosine was treated with trisodium trimetaphosphate in aqueous solution, a relatively rapid reaction occurred to form 5′-amino-5′-deoxyadenosine 5′-triphosphate, a new analog of adenosine 5′-triphosphate. The cyclic bismethylene analog of trimetaphosphate was synthesized and characterized, and acid-catalyzed ring opening reactions with this compound were performed with anhydrous methanol and anhydrous ethanol to generate the monomethyl and monoethyl esters of bis(dihydroxyphosphinylmethyl)phosphinate, respectively. Moreover, using 2′,3′-isopropylideneadenosine as the nucleophile in an analogous reaction, the synthesis of adenosine 5′-bis(dihydroxyphosphinylmethyl)phosphinate, the $\alpha,\beta:\beta,\gamma$-bismethylene analog of adenosine 5′-triphosphate, was achieved.

Ever since the early recognition of the fundamental importance of adenosine 5′-triphosphate (ATP) and other related nucleoside triphosphates in biological systems, considerable research has been directed toward developing methods for the synthesis of monoesters of triphosphoric acid.[2-6] The simplest and most direct of these is the ring opening of the trimetaphosphate anion **1** by appropriate nucleophilic reagents, as shown in eq 1. The trimetaphosphate anion is unique among the condensed inorganic phosphates in its degree of relative susceptibility to nucleophilic attack in basic media.[7] Several research groups have exploited this fact and have investigated the ring opening of salts of trimetaphosphate by various nucleophiles in aqueous solutions.[7-15] Thus, reactions



(1)

with hydroxide,[7] ammonia,[8,11] methylamine,[10] ethylamine,[10] dimethylamine,[13] and fluoride ion,[10] for example, have all led to isolable, stable salts of simple ring-opened products. In 1967, Feldmann[15] reported that trisodium trimetaphosphate reacted with strongly

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