tallized from water and crotonic acid from petroleum ether. Hydrogen peroxide was distilled under vacuum to remove any stabilizer and titrated with Ce^{4+}. Stock solutions of Fe^{2+} were determined by titration with $K_2Cr_2O_7$.

Complex formation was studied spectrophotometrically at 200–500 nm by using a Beckman 24 or Cary 1115 instrument at room temperature. Samples were prepared by mixing stock solutions and adjusting pH. Solutions were shown to be free of Fe^{3+} (which forms a more strongly absorbing complex) and used fresh or stored under N_2 to prevent oxidation. Spectra starting with ferrous perchlorate or sulfate or with ferrous ammonium sulfate were indistinguishable. The analysis of the plot in Figure 1 was made by assuming a simple ionization $Fe^{II}{\cdot}MA^{2+} \rightleftharpoons Fe^{II}MA^{+} + H^{+}$.

Reactions were carried out by slowly adding ferrous perchlorate solution (or H_2O_2) over a few minutes to stirred solutions containing the other reaction components under N_2 at room temperature, essentially as in previous papers.[3,9-11] In stoichiometric experiments, $\Delta H_2O_2/\Delta Fe^{II}$ was taken as the ratio of H_2O_2 added to Fe^{II} consumed, determined by measuring remaining Fe^{II} as its phenanthroline complex. Products were determined by gas chromatography after extraction with ether. Benzaldehyde was determined immediately and the other products first silylated with bis(trimethylsilyl)trifluoroacetamide. Products were identified by retention time, and GC–MS and all procedures were essentially those given previously.[9-11] Most separations used a 6-ft 10% OV-17 on Chromosorb W column at 160 °C with biphenyl as internal standard.

Acknowledgment. Support of this work by a grant from the National Science Foundation and a fellowship (to K.A.) from the Phillips Petroleum Company is gratefully acknowledged.

Registry No. Mandelic acid, 90-64-2; H_2O_2, 7722-84-1; $S_2O_8^{2-}$, 15092-81-6; Fe, 7439-89-6.

Stereospecific Alkyl Group Effects on Amine Lone-Pair Ionization Potentials: Photoelectron Spectra of Alkylpiperidines

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Received September 18, 1980

Abstract: Photoelectron spectra and ab initio STO-3G calculations on methylpiperidines indicate that axial 2-methyl substituents lower the amine lone-pair ionization potential (IP) by ~0.26 eV, while equatorial 2-methyl and 3- and 4-methyl substituents lower the lone pair IP by ≤0.1 eV. This establishes the mechanism of stabilization of the amine radical cation as hyperconjugative electron release, which is larger for CC bonds than for CH bonds.

The mechanism by which alkyl groups stabilize charged species is a subject of continuing interest. Because alkyl groups stabilize both cations and anions in the gas phase, a polarizability (charge, induced dipole) mechanism has gained increasing credence.[2] On the other hand, ionization potential lowering by alkyl substituents was initially attributed to inductive effects.[3] However, we have shown that the relationship between the ionization potential of a group and the lowering in ionization potential caused by alkylation is precisely that expected for hyperconjugative electron release by alkyl groups.[4] The photoelectron spectroscopic investigation of various methyl- and polymethylpiperidines reported here shows that the influence of methyl groups on amine lone-pair ionization potentials has a pronounced dependence on the stereochemical relationship between the amine lone pair and the methyl group. This dependence is only compatible with a hyperconjugative mechanism of electron release. Calculations on proton affinities indicate that alkyl groups stabilize ammonium cations in a different fashion.

Results

Photoelectron spectra of piperidine, *N*-methylpiperidine, and various ring-methylated derivatives have been measured. Figure 1 shows several representative spectra,[5] and Table I lists the amine lone-pair ionization potentials (IPs) for the piperidines studied

Table I. Ionization Potentials of Methylated Piperidines

piperidine substituent	IP_{vert},[a] eV	ΔIP_{vert},[b] eV	IP_{ad},[c] eV
	NH		
none	8.70 (8.69,[d] 8.66,[e] 8.64[f])	≡0	8.20
2-Me(eq)	8.63 (8.58[d])	−0.07	8.04
3-Me(eq)	8.63 (8.66[d])	−0.07	8.03
4-Me(eq)	8.61 (8.66[d])	−0.09	8.06
3,3-Me_2(eq, ax)	8.60	−0.10	8.05
cis-2,6-Me_2(eq, eq)	8.53	−0.17	7.93
2,2,6,6-Me_4(eq, ax, eq, ax)	8.04[g]	−0.66	7.59
	NMe		
none	8.37 (8.39,[d] 8.29[f,h])	≡0	7.80
2-Me(eq)	8.23	−0.14	7.63
3-Me(eq)	8.35	−0.02	7.76
4-Me(eq)	8.33	−0.04	7.79
4,4-Me_2(eq, ax)	8.29	−0.08	7.77
cis-3,5-Me_2(eq, eq)	8.23	−0.14	7.63
trans-3,5-Me_2(eq, ax)	8.26	−0.11	7.66
cis-2,6-Me_2(eq, eq)	8.22	−0.33	7.77
2,2,6,6-Me_4(eq, ax, eq, ax)	7.68	−0.69	7.23

[a] ±0.05 eV: previously reported values in parentheses. [b] Change in IP relative to the parent species (NH or NMe). [c] Taken as the onset of first ionization band. [d] Reference 7. [e] Reference 8. [f] Reference 9. [g] Reference 10. [h] Reference 2a.

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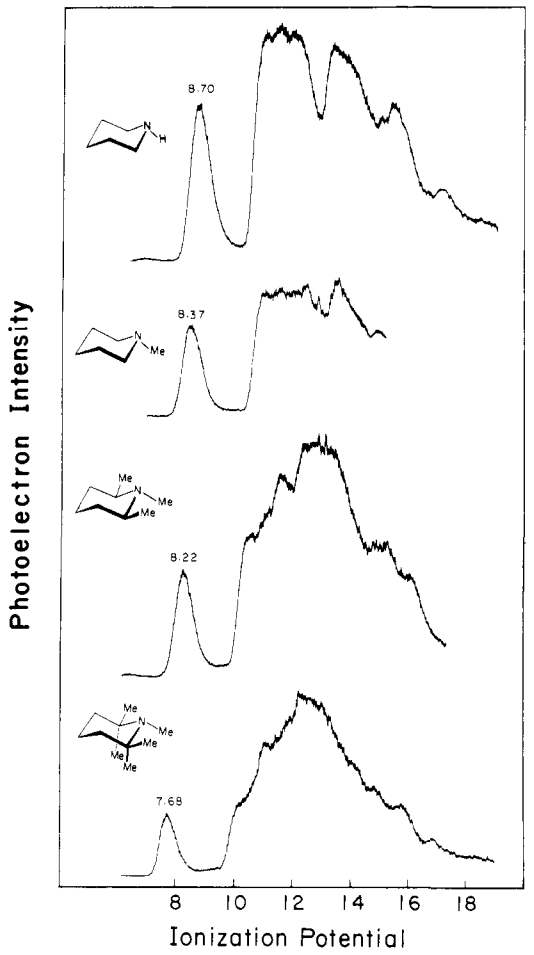

Figure 1. Photoelectron spectra of piperidine, *N*-methyl, *cis*-*N*,2,6-trimethyl-, and *N*,2,2,6,6-pentamethylpiperidines.

here, along with literature IPs[6-10] for related compounds. The IPs of secondary acylic amines and the piperidines decrease by 0.34 ± 0.07 eV upon N-methylation. Methylations at carbon result in smaller IP decreases. It has been observed previously that a single methyl substituent at the 2, 3, or 4 position of piperidine lowers the IP ≤ 0.11 eV, with the effect being the largest at the 2 position, thus suggesting a typical inductive effect.

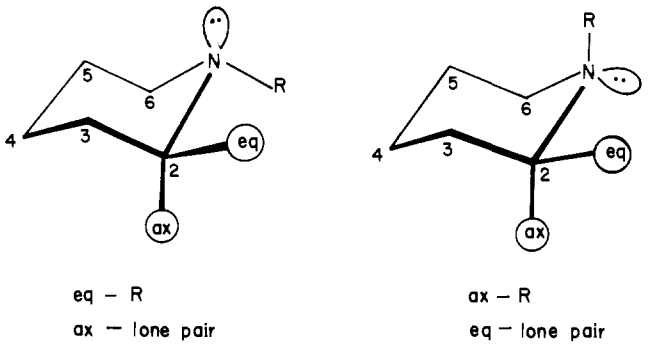

Table II. STO-3G Orbital Energies and Proton Affinities for Methylated Piperidines

piperidine substituent	equatorial NR (axial n_N) $-\epsilon$, eV	$-\Delta\epsilon^a$	PA[b] (STO-3G) kcal/mol	axial NR (equatorial n_N) $-\epsilon$, eV	$-\Delta\epsilon^a$
			NH		
none	8.02	≡0	278.5	7.67	≡0
eq-2-Me	8.01	−0.01	280.3	7.65	−0.02
ax-2-Me	7.86	−0.16	281.3	7.64	−0.03
eq-3-Me	7.99	−0.03	279.7	7.60	−0.07
ax-3-Me	8.00	−0.02	276.5	7.66	−0.01
eq-4-Me	8.00	−0.02	279.2	7.65	−0.02
ax-4-Me	7.91	−0.12	279.4	7.65	−0.02
			NMe		
none	7.78	≡0	280.9	7.41	≡0
eq-2-Me	7.76	−0.02	282.4	7.38	−0.03
ax-2-Me	7.60	−0.18	283.4	7.37	−0.04
eq-3-Me	7.75	−0.03	282.0	7.35	−0.06
ax-3-Me	7.75	−0.03	278.7	*c*	*c*
eq-4-Me	7.76	−0.02	281.6	7.39	−0.02
ax-4-Me	7.69	−0.09	281.8	7.38	−0.03

[a] Relative to the parent (NH or NMe). [b] Experimental proton affinities are 225.4 and 228.8 kcal/mol for piperidine and *N*-methylpiperidine, respectively: Aue, D. H.; Bowers, M. T. in "Gas Phase Ion Chemistry"; Academic Press, 1979; Vol. 2, pp 1-51. [c] Using standard geometries, the 1,3-diaxial Me-Me interaction is unrealistically large for this calculation to be meaningful.

However, we find no systematic distinction between a single methyl substituent at carbons 2, 3, or 4 of piperidine; each type of methyl decreases the amine IP by 0–0.1 eV. These *C*-methyl substituents occupy equatorial positions in the chair conformation of piperidine.[11] Substituting an additional equatorial methyl group to form *cis*-2,6-dimethylpiperidine or *cis*-3,5-dimethylpiperidine results in a nearly additive decrease in IP. Similar effects are observed with *N*-methylpiperidines.

Substituting an axial methyl group at the 3 or 4 position also has a very small effect, as demonstrated by the IPs of 3,3-dimethylpiperidine, *trans*-1,3,5-trimethylpiperidine, and 1,4,4-trimethylpiperidine. Assuming that the substituent effects are additive, 2-, 3-, or 4-equatorial and 3- or 4-axial methyl substituents lower the IP of piperidine or the *N*-methyl derivative by 0.07 ± 0.07 eV per methyl group.

By contrast, 2- and 6-axial methyl substituents cause a very large nitrogen lone-pair IP decrease. The substitution of two axial methyl groups on *cis*-2,6-dimethylpiperidine to form 2,2,6,6-tetramethylpiperidine lowers the amine lone-pair IP by 0.49 eV. Similarly, in the *N*-methyl analogues, a 0.54-eV decrease is observed. Each α-axial 2-methyl substituent lowers the IP by 0.26 ± 0.02 eV.

The nearly identical influence of *C*-methyl substituents on amine IPs in the piperidines and *N*-methylpiperidines implies that the conformations at nitrogen are identical in all these species. The conformational preference of both piperidine and *N*-methylpiperidine has been debated for many years.[12-14] Gas-phase and nonpolar solvent studies indicate a 60–70% preference for an axial lone pair at 25 °C in piperidine,[12,13] while NMR data in methanol suggest a slight preference for an equatorial lone pair.[14] For

(5) Photoelectron spectra were recorded on a Perkin-Elmer PS-18 photoelectron spectrometer using argon and xenon as internal calibrants. Resolution was 20–25 meV.

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(12) Blackburne, I. D.; Katritzky, A. R.; Takeuchi, Y. *Acc. Chem. Res.* **1975**, *8*, 300.
(13) The paper by Vierhapper and Eliel [Vierhapper, F. W.; Eliel, E. L. *J. Org. Chem.* **1979**, *44*, 1081] contains an excellent critical evaluation of N-Me and N-H conformational preferences in piperidines and decahydroquinolines. Eliel, E. L.; Vierhapper, F. W. *J. Am. Chem. Soc.* **1975**, *97*, 2424. Crowley, P. J.; Robinson, M. J. T.; Ward, M. G. *Chem. Commun.* **1974**, *825*.
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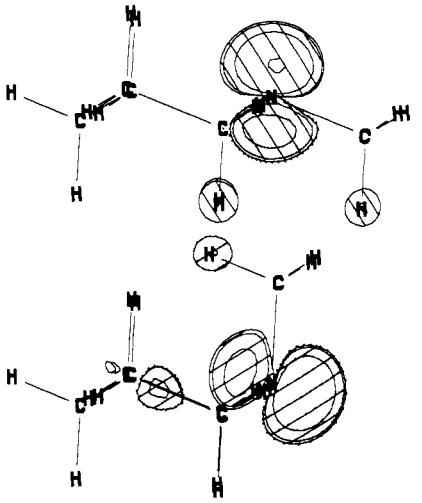

Figure 2. Orbital contour plots of equatorial and axial *N*-methylpiperidines.[16]

N-methylpiperidine, the axial lone-pair preference is on the order of 99%.[13]

STO-3G calculations[15,16] (Table II) indicate that the equatorial NH is favored by 1.0–1.9 kcal/mol over the axial, while the equatorial NMe is favored by 5.4–10.8 kcal/mol. The experimental trend in ionization potentials is reproduced by calculations on the equatorial NH and NMe species but not by calculations on the axial NH and NMe conformers. Axial lone-pair IPs are predicted to be lower than those of equatorial lone-pair IPs, and the latter are unaffected by alkylation on carbon. The axial lone-pair IP is influenced most by an axial 2-methyl substituent.[17] Thus, theory supports the experimental deduction that an axial 2-methyl lowers an amine lone-pair IP much more than all other methyls on carbon.

Discussion

Inductive electron donation by methyls cannot explain these observations, since inductive effects should be dependent on the number of bonds separating the substituent and the lone pair, not on the substituent stereochemistry. If polarizability were the dominant factor in these compounds, a much larger effect would have been observed for the axial 3-methyl substituents in 3,3-dimethylpiperidine and *trans*-1,3,5-trimethylpiperidine, since this group should be relatively close to the (axial) lone pair. Furthermore, a 2-equatorial methyl is closer to the axial lone pair than a 2-axial methyl, and since polarizability depends on r^{-4}, where r is the distance between the charge in the radical cation and the group in which a dipole is induced, an equatorial methyl should stabilize the radical cation (lower the IP) more than an axial methyl. The opposite is observed experimentally.

The large effect of 2- and 6-axial methyl substituents is compatible only with a hyperconjugative mechanism of stabilization of the amine radical cation. The stereochemical dependence found experimentally indicates that the σ_{CC} orbital is a more potent hyperconjugative donor than a σ_{CH} orbital. Orbital contour plots shown in Figure 2[17] show the significant mixing of the amine lone pair and 2-axial bonds in piperidine. The lower calculated IP of piperidines with axial NH or NMe can also be attributed to the ring CC hyperconjugation with the amine lone pair (Figure 2).

This conclusion is a contrast to the conclusion by Cieplak, that hyperconjugative electron donation by σ_{CH} bonds is larger than that by σ_{CC} bonds.[18] Although the phenomenon discussed by Cieplak is admittedly different from that studied here, we see no obvious reason for the opposite order of electron release to the σ^* orbital of a partially formed bond (Cieplak) or to a half-occupied n orbital (this work).

Finally, we contrast the dominance of hyperconjugation in influencing IPs with the polarizability model which is so successful for rationalizations of proton affinity (PA) magnitudes.[2] The calculated PAs of the piperidines are given in Table II. Although these PAs are 52–53 kcal/mol too high, relative values should be reasonable at this level. Although the PA of N, axial-2-dimethylpiperidine is 1 kcal/mol larger than that of the 2-equatorial methyl compound, there is an additional Me–H(N^+) gauche interaction in the latter, which overrides the expected greater stabilization of piperidinium by an equatorial 2-methyl substituent.[16]

The stereospecificity of alkyl group effects on lone-pair (or π) IPs is presumably general and should have significant chemical consequences, since IPs are related to nucleophilic reactivities of a variety of compounds. Similar studies for other functional groups will be reported at a later date.

Acknowledgment. We are grateful to the National Institute of Drug Abuse for financial support of this research, Professor John D. Roberts for samples of many of the piperidines, and Professors D. H. Aue and E. L. Eliel and Dr. Salvatore Profeta for helpful discussions.

Registry No. 2-methylpiperidine, 109-05-7; 3-methylpiperidine, 626-56-2; 4-methylpiperidine, 626-58-4; 3,3-dimethylpiperidine, 1193-12-0; *cis*-2,6-dimethylpiperidine, 766-17-6; 2,2,6,6-tetramethylpiperidine, 768-66-1; 1,2-dimethylpiperidine, 671-36-3; 1,3-dimethylpiperidine, 695-35-2; 1,4-dimethylpiperidine, 695-15-8; 1,4,4-trimethylpiperidine, 1003-84-5; *cis*-1,3,5-trimethylpiperidine, 14446-76-5; *trans*-1,3,5-trimethylpiperidine, 16544-52-8; *cis*-1,2,6-trimethylpiperidine, 2439-13-6; 1,2,2,6,6-pentamethylpiperidine, 79-55-0; piperidine, 110-89-4; *N*-methylpiperidine, 626-67-5.

(15) The program GAUSSIAN 70 (Hehre, W. J.; Lathan, W. A.; Ditchfield, R.; Newton, M. D.; Pople, J. A. *QCPE* **1973**, *236*) was used for these calculations. The geometries were based on the crystal structure of piperidine·H_2S: Smail, E. J.; Sheldrick, G. M. *Acta Crystallogr., Sect. B* **1973**, *B29*, 2027. Standard methyl substituents were used to replace the appropriate hydrogen in calculations on the substituted derivatives.

(16) The anomalously large axial-4-Me effect must arise from the unrealistically close approach of the axial-4-Me to the 2-axial hydrogens.

(17) We thank Professor William L. Jorgensen for the program used to generate these plots.

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