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COMMENTS ON STERIC EFFECTS IN BUTTRESSED METHYL PYRIDINE SPECIES

JOHN C. SCHUG AND JIMMY W. VIERS

Department of Chemistry
Virginia Polytechnic Institute and State University
Blacksburg, VA 24061

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ABSTRACT -Using MINDO/3 calculations, we have investigated the importance of gear effects and pointing H-H interactions in several polymethyl-pyridine systems. Gear clashing of methyl groups on adjacent ring positions was found to produce about 0.6 kcal mole^{-1} stabilization, while interaction between two pointing hydrogens destabilizes the molecule by about 1.1 kcal mole^{-1}. Calculated barriers for rotation of the isopropyl group in several 1-isopropyl-polymethyl pyridinium cations were in good agreement with experimental results published recently by Roussel *et al*. The calculations indicate that the decrease in the rotational barrier upon additional buttressing of methyl groups can be attributed to destabilization of the ground rotational conformer for the more sterically hindered 1-isopropyl polymethyl pyridinium species.

In a recent publication Roussel *et al*[1] made a very interesting comparison of the steric properties of methyl groups with respect to reaction kinetics on one hand and internal rotational barriers on the other. The kinetics data discussed were quaternization rates of methylpyridines, and the effects of the methyl substituents were understandable in terms of buttressing when two adjacent ring positions contained methyl groups. The rotational barriers discussed were for rotation of isopropyl groups in a series of methylated-isopropyl pyridine species. At first it appeared paradoxical that buttressed methyl groups seemed to have a smaller "effective size" than unbuttressed ones, and that the presence of additional methyl groups in buttressing positions effected decreases in the rotational energy barriers. However, Roussel *et al* rationalized their findings by (a) appealing to the preference of adjacent methyl groups to exist in a "gear-clashed" conformation and (b) suggesting that the decreases in the barrier heights arise because the more sterically hindered compounds become increasingly unable to relieve steric strain in the lowest energy rotamers.

It is of considerable interest to attempt a more quantitative examination of these findings. The steric effects on quaternization rates are well understood. They are in agreement with earlier observations and have been well explained by theoretical studies.[2] Therefore, the following comments will concentrate on the rotational studies.

Our successful earlier studies[2] on pyridines and pyridinium cations were based on the semi-empirical all-valence-electron MINDO/3 method,[3] and we have continued to use it in the present study. In addition to studying the structures and rotational barriers involved, the present calculations provide additional support for the utility of the MINDO/3 method. We employed the

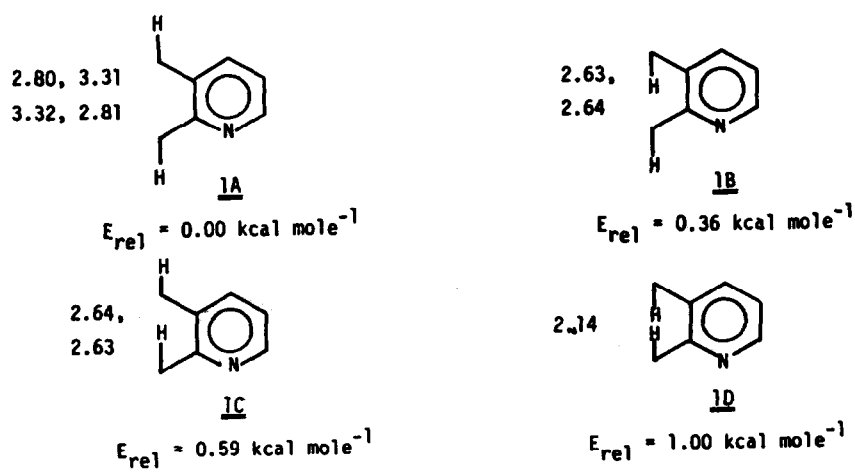
GEOMO/RV program[4] which incorporates Rinaldi's[5] geometry optimization scheme. In all cases optimization was carried out with no constraints, except for fixing a single dihedral angle when necessary for the purpose of generating rotational barriers.

Since the discussion of Roussel et al[1] rests heavily on the preference of two adjacent methyl groups for the "gear-clashed" conformation, we began by examining the four rotamers of 2,3-lutidine (1) shown in Fig. 1. Conformation A was found to have the lowest energy, it being more stable by 0.3, 0.6, and 1.0 kcal mole^{-1} than conformations B, C, and D, respectively. Since all bond-lengths and bond angles were found to be essentially constant throughout the series A-D, there are no obvious bonding effects which account for the energy differences. It is tempting to conclude that the non-bonded H-H interactions are responsible for the relative energies. The nearest H-H distances are tabulated on Fig. 1 for the four rotamers. In D the single pair of interacting hydrogens is separated by 2.14A, which is less than the sum of two hydrogen-atom van der Waals radii. In A the distances are larger than in B and C, and in all three cases the distances are larger than two van der Waals radii. One could say that the sum of the four weaker interactions in A is more stabilizing than the sum of two interactions in B or C. Unfortunately, these interactions cannot be identified from the MINDO/3 calculations. The "bonding interactions" attributed to all pairs of neighboring methyl-group hydrogens are found to be repulsive in nature. Those calculated for A are smaller than those for B or C; but that calculated for D is the least repulsive of the set. There is in fact no one term which can be singled out from the MINDO/3 calculations as being responsible for the differences in total energy. This is not surprising, considering that we are dealing with a total energy range of 1 kcal mole^{-1}. The results are, however, in agreement with molecular mechanics[6] and CNDO/2 calculations,[7] as well as with experimental observation for the case of ortho-xylene.[8]

Roussel et al[1] concluded that the "effective size" of a buttressed methyl group appears to be smaller than the "effective size" of a non buttressed methyl. These conclusions were based on the observations of conformer population data for compounds 2-4 (Figure 2) obtained from lineshape analysis of NMR spectra of these compounds. Note that the more stable conformer in each case has the larger face of the isopropyl substituent (consisting of two methyls) directed toward the buttressed methyl, which might imply that the buttressed methyl has a smaller "effective size".

To obtain a more complete picture of the energetics involved, we used the MINDO/3 algorithm to consider four subcases for each conformer of compound 2; these are designated 2A1 through 2A4 and 2B1 through 2B4. The energies obtained for all eight rotamers considered are shown in Fig. 3. The preference for conformer A was attributed by Roussel, et al[1] to the preference for a gear clashed conformation for methyl substituents on adjacent ring positions. The gear clashed conformation for the methyls at 2 and 3 cause the isopropyl group to see a "pointing H" i.e., a H on the 2-methyl

Figure 1. Energies of Rotational Conformers of 2,3-Lutidine (1). Distances between nearest methyl hydrogens are indicated.

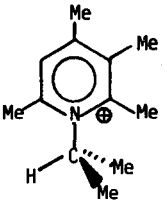
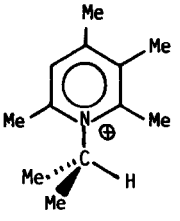
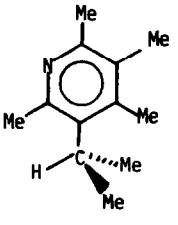
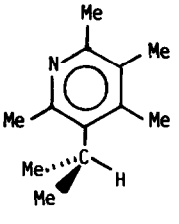
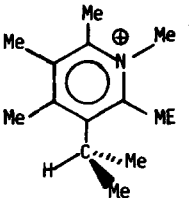
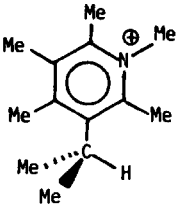


group is locked in the plane of the ring pointing toward the 1-isopropyl substituent. To avoid a 1,2-frontal interaction of the H on the isopropyl group with this "pointing H" at 2, the more stable conformer has the isopropyl H directed toward position 6. The unbuttressed methyl at 6 has a smaller barrier to rotation than does the methyl at 2; it is therefore not locked and can avoid a 1,6-frontal interaction with the isopropyl H by rotation of the methyl such that the hydrogens on the 6-methyl make dihedral angles (H-$C_{6\alpha}$-C_6-N) of ± 60°. When the isopropyl H is directed toward the buttressed methyl at position 2 in conformer 2B, relief of the 1,2-frontal H interaction is at the expense of larger steric hindrance experienced by rotation of the buttressed methyl at 2. Conformer 2A1 is the most stable. Our MINDO/3 calculations confirm the arguments of Roussel et al.[1] Within each subset of four conformers, the most stable rotamers are those in which an α-β frontal interaction of two H atoms is avoided. Thus, 2A1 is more stable than 2A3 and 2A4 because of the advantageously locked methyl groups at positions 2 and 3. The two highest energy forms (2A2 and 2A4) are destabilized chiefly by the pointing interactions involving the 6-methyl group. The overriding importance of this interaction is graphically seen in 2B, where the two least stable forms have locked methyls at 2 and 3, but are destabilized by the pointing interaction with the 2-methyl group.

Two factors are important in determining the relative stabilities of the various rotamers for this compound. One is the gear clashing effect of methyls substituted at adjacent positions on the pyridine ring, which produces stabilization. The second is the 1,2 or 1,6 frontal interactions of hydrogens locked in the plane of the ring. Such frontal interactions result in a destabilizing effect for rotamers exhibiting this behavior. The magnitude of these two effects is difficult to sort out in 2 due to the presence of the additional methyl at position 4. Locking of the two methyls at 2 and 3 in the gear clashed arrangement gives rise to an unlocked (gear meshed) conformation between methyls at 3 and 4. Similarly, unlocking at 2 and 3 results in locking at 3.

In order to isolate the quantitative effects contributed by adjacent ring position gear clashing and the α,β frontal interaction of hydrogens, we have examined the stabilities of some of

Figure 2. Populations[a] of Rotational Conformers

Compound	Population	Conformer A	Population	Conformer B
1-Isopropyl-2,3,4,6-tetramethylpyridinium ion (2)	0.77		0.23	
3-Isopropyl-2,4,5,6-tetramethylpyridine (3)	0.69		0.31	
1,2,4,6-tetramethyl-3-isopropylpyridinium ion (4)	0.80		0.20	

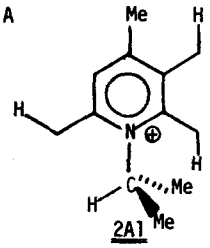
[a]From reference 1

the important rotamers of the 1-isopropyl-2,3,6-trimethylpyridinium ion (5). Energies of these rotamers are given in Figure 4. A comparison of 5A1 with 5A2 or of 5A3 with 5A4 indicates that the 1,6 frontal interaction results in a destabilization of 1.1 kcal mole^{-1}. Comparison of 5A1 with 5A3 or of 5A2 with 5A4 indicates that the gear clashed conformation adds about 0.6 kcal mole^{-1} of stabilization energy. Although gear clashing of methyl groups at adjacent positions on the ring is an important contributor to the stabilities of the rotamers, the more important contribution is the avoidance of the α,β frontal interaction of hydrogens in the most stable rotamers.

The most interesting result of Roussel et al[1] involved the relative rotational barrier heights

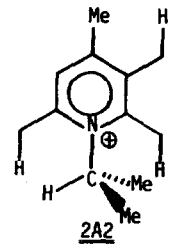
Figure 3. Energies of Rotational Conformers for the 1-Isopropyl-2,3,4,6-tetramethylpyridinium Cation

Conformer A



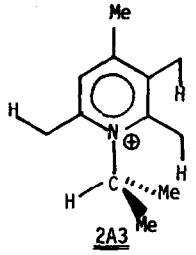
2A1

E_{rel} = 0.00 Kcal mole^{-1}



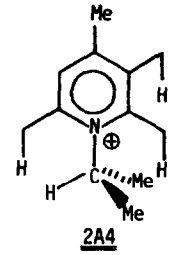
2A2

E_{rel} = 1.47 Kcal mole^{-1}



2A3

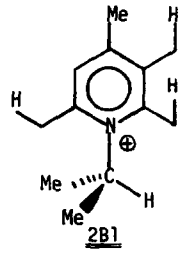
E_{rel} = 0.25 Kcal mole^{-1}



2A4

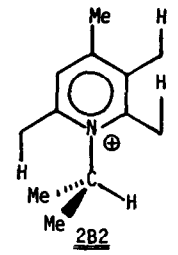
E_{rel} = 1.32 Kcal mole^{-1}

Conformer B



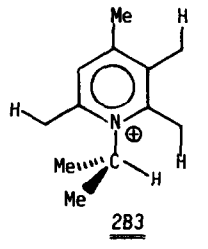
2B1

E_{rel} = 0.78 Kcal mole^{-1}



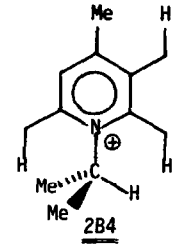
2B2

E_{rel} = 1.04 Kcal mole^{-1}



2B3

E_{rel} = 1.26 Kcal mole^{-1}



2B4

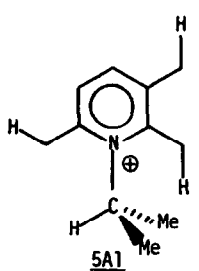
E_{rel} = 1.33 Kcal mole^{-1}

for the isopropyl groups in cations: 1-isopropyl-2,4,6-trimethylpyridinium (6), 1-isopropyl-2,3,4,6-tetramethylpyridinium (2), and 1-isopropyl-2,3,4,5,6-pentamethylpyridinium (7). Additional buttressing was found to decrease the rotational barrier heights. Our calculated barriers are compared to the experimental results in Table I. If τ represents the $HC_{N\alpha}NC_2$ dihedral angle, all three cations were found to have energy minima at τ=0° (rotational ground state, GS) and maxima at τ=90° (rotational transition state, TS). The calculated barriers are of the correct magnitude, and the three compounds are correctly ordered, but the overall range of barrier heights is calculated to be somewhat greater than the experimental range.

Cation 2 has a subsidiary minimum at τ=180°. The energy difference, E(180°)-E(0°), was found to be 0.778 kcal mole^{-1}. This energy difference is slightly too large in comparison with experiment, for it would yield a Boltzmann factor, exp(-ΔE/RT), of 0.251 at 10°C and 0.132 at -80°C for the relative population of these two rotamers. Roussel et al[1] report a relative population of 0.23/0.77 = 0.30. Again, it is not surprising that such a small energy difference is slightly overestimated by the calculations. We do wish to note that it is rather surprising that Roussel et al[1] find "no dramatic changes... over a large range of temperatures for the populations." For the -80° to 10°C temperature range studied, the relative population would be expected to change by about 50%.

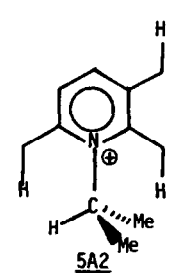
The optimized geometries obtained for the minimum (GS) and maximum (TS) energy rotamers are rather interesting and deserve some comment. Table II shows the main bond lengths and Table III the bond angles for all six species. If one looks only at these numbers, he concludes that only nominal changes take place during rotation of the isopropyl groups. On going from the minimum to the maximum energy rotamers, the chief changes are that the internal ring angle at the nitrogen closes down by several degrees; the bond lengths, d_{NC} and d_{NC} increase very slightly; the $NC_{N\alpha}C_{N\beta}$ angles of the isopropyl substituent increase by about 2 degrees and the $NC_{N\alpha}H$ angles of the isopropyl group decrease slightly.

Figure 4. Energies of Rotational Conformers of 1-Isopropyl -2,3-6-trimethylpyridinium ion (5)



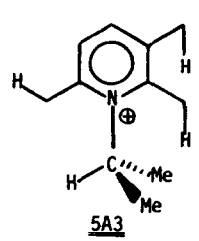
5A1

E_{rel} = 0.00 Kcal mole^{-1}



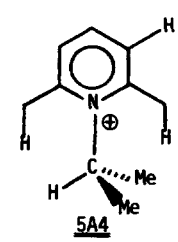
5A2

E_{rel} = Kcal mole^{-1}



5A3

E_{rel} = 0.61 Kcal mole^{-1}



5A4

E_{rel} = 1.75 Kcal mole^{-1}

Much more interesting changes are observed in the dihedral angles, some of which are listed in Table IV. In their low energy rotamers species $\underline{6}_{GS}$ and $\underline{2}_{GS}$ have all ring atoms and all attached carbon atoms essentially co-planar. In the high-energy rotamers $\underline{6}_{TS}$ and $\underline{2}_{TS}$ these cations experience considerable twisting, however. The exocyclic carbons are forced out of the plane of the rings, and the aromatic systems even become non-planar. As Roussel et al argued, cation $\underline{7}$ is quite strained even in the most stable rotamer. Our calculated results are in agreement with the argument by Roussel et al that the decrease in rotational barriers ($\underline{6} > \underline{2} > \underline{7}$) can be attributed to "a better accomodation of the strain in the transition state than in the ground state" on going from the trimethyl substituted to the pentamethyl substituted species. $\underline{7}_{GS}$ is obviously non-planar, and becomes even more non-planar in the high-energy rotamer ($\underline{7}_{TS}$). The non-planarity of $\underline{7}_{GS}$ should be observable by x-ray diffraction in the absence of any unusual counter ion or crystal packing effects if single crystals could be grown.

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Table I. Calculated and Experimental Rotational Barriers

Cation	Calcd. $\Delta E^{\ddagger}$/(kcal mole)$^{-1}$	Exptl.$\Delta G^{\ddagger}$/(kcal mole)$^{-1}$
$\underset{\sim}{6}$	15.73	15.97
$\underset{\sim}{2}$	13.54	15.04
$\underset{\sim}{7}$	10.51	13.89

Table II. Calculated Distances (Angstroms) for Methylated N-isopropyl-pyridinium Ions, Rotational Ground States and Transition States

Distance	^{6}GS	^{6}TS	^{2}GS	^{2}TS	^{7}GS	^{7}TS
N-C_2	1.394	1.398	1.390	1.400	1.387	1.391
N-C_6	1.388	1.395	1.389	1.388	1.388	1.392
C_2-C_3	1.413	1.413	1.444	1.437	1.439	1.436
C_2-$C_{2\alpha}$	1.501	1.499	1.504	1.501	1.504	1.501
C_3-$C_{3\alpha}$	-	-	1.504	1.502	1.506	1.503
C_3-C_4	1.419	1.422	1.442	1.448	1.441	1.447
C_4-$C_{4\alpha}$	1.489	1.488	1.496	1.493	1.502	1.497
C_4-C_5	1.417	1.419	1.415	1.416	1.440	1.446
C_5-$C_{5\alpha}$	-	-	-	-	1.506	1.504
C_5-C_6	1.417	1.415	1.410	1.413	1.441	1.435
C_6-$C_{6\alpha}$	1.500	1.498	1.501	1.497	1.506	1.502
N-C_{N_α}	1.509	1.513	1.513	1.513	1.514	1.514
C_{N_α}-C_{N_β}	1.521	1.526	1.521	1.526	1.521	1.526
C_{N_α}-C_{N_β}'	1.519	1.523	1.519	1.523	1.520	1.524
C_{N_α}-H	1.135	1.134	1.136	1.134	1.135	1.134

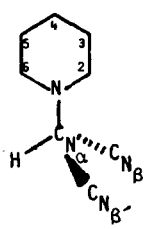

Table III. Calculated Angles (Degrees) for Methylated N-isopropylpyridinium Ions, Rotational Ground States and Transition States

Angle	^6GS	^6TS	^2GS	^2TS	^7GS	^7TS
C_2NC_6	120.9	117.4	121.5	117.6	121.8	117.7
NC_2C_3	118.1	117.4	120.8	119.7	120.0	118.4
$C_2C_3C_4$	125.5	125.1	119.7	118.7	119.9	118.9
$C_3C_4C_5$	112.0	111.1	115.1	114.2	117.9	116.5
$C_4C_5C_6$	125.3	124.9	124.8	125.0	120.1	119.0
C_5C_6N	118.2	117.5	117.0	116.0	119.7	118.4
$NC_2C_{2\alpha}$	125.2	123.7	121.2	119.1	121.8	119.5
$C_2C_3C_{3\alpha}$	-	-	119.7	119.7	118.7	118.6
$C_3C_4C_{4\alpha}$	124.0	124.7	125.4	125.5	121.0	121.7
$C_6C_5C_{5\alpha}$	-	-	-	-	118.7	118.5
$NC_6C_{6\alpha}$	123.5	122.8	124.4	124.3	122.6	119.2
$C_2NC_{N\alpha}$	121.3	121.2	121.8	120.9	119.8	121.5
$C_6NC_{N\alpha}$	117.8	121.4	116.6	121.4	118.3	120.7
$NC_{N_\alpha}C_{N_\beta}$	114.1	116.5	114.4	116.2	114.3	116.4
$NC_{N_\alpha}C_{N_\beta}'$	114.2	116.6	114.4	116.4	114.7	115.7
$NC_{N_\alpha}H$	104.7	103.8	104.5	104.3	104.8	104.7

Table IV. Calculated Dihedral Angles (Degrees) for Methylated N-isopropylpyridinium Ions, Rotational Ground States and Transition States

Dihedral angle	^6GS	^6TS	^2GS	^2TS	^7GS	^7TS
$\tau(NC_2C_3C_4)$	0.7	149.2	0.1	6.2	0.6	7.5
$\tau(NC_6C_6C_4)$	0.3	149.5	0.1	11.5	2.0	8.0
$\tau(C_2C_3C_4C_5)$	0.8	8.7	0.2	10.8	6.9	17.2
$\tau(C_6C_4C_4C_3)$	0.5	9.0	0.1	13.8	7.6	17.0
$\tau(C_3C_4C_5C_6)$	0.5	9.0	0.1	13.8	7.6	17.0
$\tau(C_5C_4C_3C_2)$	0.8	8.7	0.2	10.8	6.9	17.2
$\tau(C_{N\alpha}NC_2C_3)$	179.7	149.3	179.1	143.8	172.9	141.6
$\tau(C_{N\alpha}NC_6C_5)$	179.4	149.5	179.1	147.1	173.5	141.3
$\tau(C_{N\alpha}NC_2C_{2\alpha})$	0.8	38.6	1.3	42.3	8.1	43.5
$\tau(C_{N\alpha}NC_6C_{6\alpha})$	1.0	36.1	1.3	37.7	5.6	43.6
$\tau(C_{2\alpha}C_2C_3C_4)$	179.7	163.3	179.7	162.3	179.7	167.2
$\tau(C_{6\alpha}C_6C_5C_4)$	179.9	166.0	179.6	169.2	177.2	166.9
$\tau(C_{2\alpha}C_2C_3C_{3\alpha})$			0.2	16.4	3.0	11.8
$\tau(C_{3\alpha}C_3C_2N)$			179.8	169.9	177.9	173.3
$\tau(C_{3\alpha}C_3C_4C_{4\alpha})$			0.3	9.3	7.6	19.2
$\tau(C_{4\alpha}C_4C_3C_2)$			179.8	172.1	172.5	162.2