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GEAR EFFECT—10

CONFORMATIONAL ASPECTS OF THE POSITIVE OR NEGATIVE BUTTRESSING EFFECTS OF METHYL GROUPS: POLYMETHYLPYRIDINES

CHRISTIAN ROUSSEL,*[1a] ALEXANDRU T. BALABAN,[1b] ULF BERG,[1c] MICHEL CHANON,[1d] ROGER GALLO,[1a] GERD KLATTE,[1a] JOSEPH A. MEMIAGHE,[1a] JACQUES METZGER,[1a] DANIELA ONICIU,[1b] and JOHANNA PIERROT-SANDERS[1a]

I.P.S.O.I., Centre Universitaire Saint-Jérôme, Rue Henri-Poincaré, 13013 Marseille, France; Polytechnic, Bucharest, Roumania; Organic Chemistry 3, Chemical Center, University of Lund, P.O. Box 740, S-22007 Lund, Sweden

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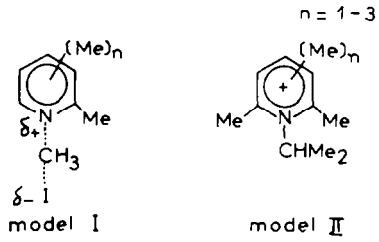
Abstract—The effect of the shape of a methyl group on reactivity, which cannot be accounted for by considering a methyl group as a spherical substituent with the appropriate van der Waals radius, was considered in kinetics of alkylation of substituted pyridines and barriers to rotation and ground state conformations of an isopropyl group attached to a planar framework. The perturbation of a methyl group by an o-methyl group is accounted for by a unique conformational explanation which involves the polyhedral shape of the methyl group.

Much work has been devoted to the quantitative treatment of the steric requirement of substituents,[2] and various steric scales have been proposed in aliphatic (E_s and derived scales E_s^o, E_s^c, E_s^e, υ, E_s' and E_s'')[2-8] and heteroaromatic molecules (S^o).[9] However, in complex systems the steric requirement of groups could be largely modified by conformational and/or angular effects when several groups are in interaction.[10-12] With spherical, conical or cylindrical substituents the major mode of strain accommodation will be bond bending as exemplified by iodine substituent in the biphenyl series.[13a] With polyhedral substituents, the primary mode will usually be rotation of the groups,[13b] although in addition bond bending and other modes will also contribute, as exemplified by isopropyl group conformational state in model thiazoline-2-thiones.[11b]

The methyl group stands as a challenge, since it is the smallest polyhedral alkyl substituent which can be involved, conceptually, in static or dynamic gearing. Furthermore, its intimate behaviour, which is actually a matter of controversy,[14-16] is of primary importance since it is often taken as a reference for the size of the alkyl groups. Recently Mislow *et al.*[16] in an answer to the question "Is the effective size of an alkyl group a gauge of dynamic gearing?" concluded that "It remains to be convincingly demonstrated that gear or cogwheel effects play a significant role in determining the effective size of alkyl groups in rate processes".

In fact, keeping in mind that the "three-pronged" nature of the methyl group[16] (geometrical concept) is well documented, various levels of information can be reached from the point of view of the determination of its effective size (energy concept). The first level is that a methyl group can be treated as a spherical substituent (or strictly a substituent with local $C_{\infty v}$ symmetry) with the appropriate van der Waals radius. The second level is that the effective size of the methyl is conformationally dependent: such a relation between the effective size and the conformation implies that the steric anisotropy of the methyl is such that it cannot be considered as spherical and described by one van der Waals radius. The third level is that the determination of the effective size of the methyl group is by some way related to the "gear effect"; i.e. the methyl group acts as a small gear and is able to induce interlocked conformational states, which are evidenced in the determination of its effective size. In this study we report two classical situations[17] which are used for the experimental determination of the steric requirement of groups: (a) kinetics of alkylation of substituted pyridines (Model I); (b) barriers to rotation and conformational state of an isopropyl group attached to a planar framework (Model II), and apply them to the determination of the effective size of the methyl group.



Scheme 1.

The aim of this communication is to see which of the three descriptions of the methyl group is best suited to account for the experimental facts. Our approach to the problem is to analyze how a methyl group in the vicinity of a reactive center (nitrogen of the pyridine; Model I) or in the vicinity of a conformationally mobile center (isopropyl group; Model II) reacts to the perturbing effect of substitution in the β-position. Does it react as a three-pronged substituent (for which the main mode of accommodation of the extra steric strain will be through torsion) or as a spherical one (for which the only mode will be bond bending or stretching)? If it reacts as a three-pronged substituent is the gear effect involved?

RESULTS

(A) *Steric requirement of the methyl group from kinetics of alkylation of substituted pyridines*

The Menschutkin reaction applied to substituted pyridines is particularly suitable for the quantitative study of

Table 1. Rate constants for the quaternization of polymethyl pyridines by methyl iodide in acetone

	Methylpyridine	pKa	$k_{298} \times 10^6$	k_x/k_H	log k_{rel}
1	H	5.19	229	1	0
2	2	5.96	86	0.376	-0.43
3	3	5.68	338	1.48	0.17
4	4	6.02	453	1.98	0.30
5	3,4	6.50	661	2.89	0.46
6	3,5	6.15	521	2.28	0.36
7	2,3	6.56	77	0.336	-0.47
8	2,4	6.80	150	0.655	-0.18
9	2,5	6.55	148	0.646	-0.19
10	2,6	6.72	9	0.0393	-1.41
11	2,3,5	7.15	149	0.651	-0.19
12	2,3,6	7.40	6	0.026	-1.58
13	2,4,6	7.63	18	0.078	-1.11
14	2,3,4,6	8.10	7.07	0.031	-1.51
15	2,3,5,6	7.91	2.92	0.013	-1.89
16	2,3,4,5,6	8.75	3.5	0.015	-1.82

electronic, steric and solvent effects on an S_N2 reaction, and several recent reports have stressed the various advantages of the use of azaromatics for this type of studies.[18-20] One of the main advantages is the separation of electronic and steric effects by the comparison of basicity and nucleophilicity.

The second order rate constants of the quaternization by methyl iodide in acetone are given in Table 1 for pyridine and 15 methylpyridines; the reported values at 298 K are derived from Eyring plots fed with 3 to 9 (usually 5) precise rate constant determinations by conductometric method, performed at *ca* 20°, *ca* 25° and *ca*

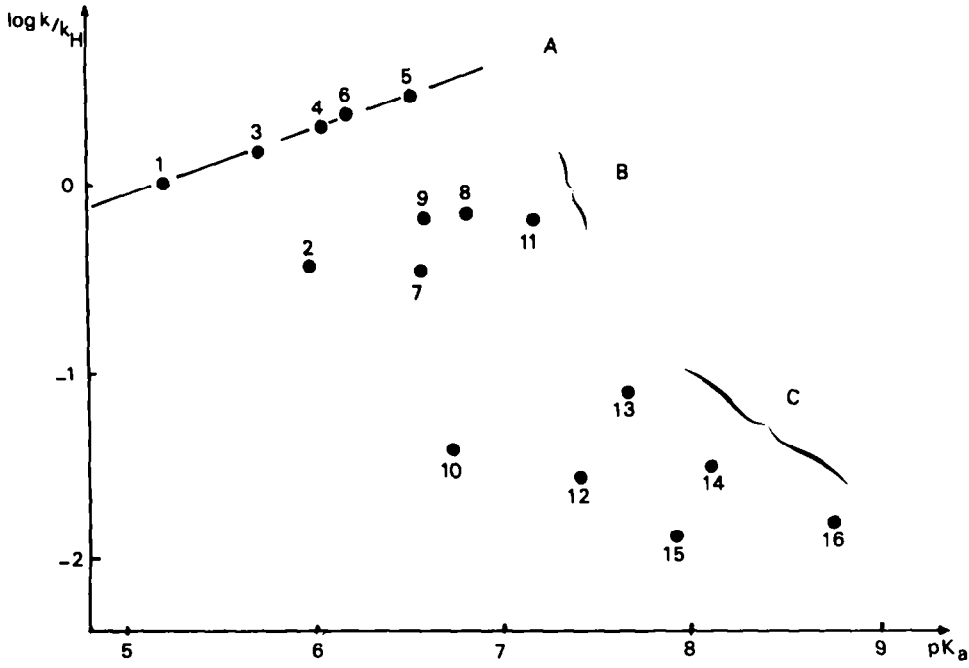


Fig. 1. Brønsted plot for the quaternization of polymethylpyridines by methyl iodide at 25° (solvent acetone). For the number identification see Table 1. Set A; pyridines with positions 2 and 6 free; Set B: pyridines with one methyl position 2; Set C: pyridines with two methyl groups in positions 2 and 6.

30° (maximum error 1.3%, for experimental data see Ref. 21).

The rate constants vary from $2.9 \cdot 10^{-6}\,M^{-1}s^{-1}$ for 2,3,5,6-tetramethylpyridine to $661 \cdot 10^{-6}\,M^{-1}s^{-1}$ for 3,4-dimethylpyridine while the pKa values vary from 5.19 for unsubstituted pyridine to 8.75 for pentamethylpyridine. The pKa values have been shown to be additive using increments derived from 2-methyl, 3-methyl and 4-methyl up to the pentamethyl compound.[22] It results from this additivity that steric effects are not operating in the pKa[23] values of the studied compounds. Rate constants and pKa values are given in Table 1.

The plot of log (k_R/k_H) (k_R stands for the rate constant of a given R-substituted pyridine, k_H stands for pyridine itself) against pKa is shown in Fig. 1; no straight forward relationship is apparent if one considers the whole group of points.

If one group structures which show some similarity in the geometrical relationship between the nucleophilic center and its surrounding, the whole set of compounds parts into three main classes: pyridines with positions 2 and 6 free (set A, 5 compounds), pyridines with one methyl group in position 2 and with position 6 free (set B, 5 compounds), and pyridines with both positions 2 and 6 occupied by a methyl group (set C, 6 compounds; Fig. 1).

Compounds belonging to set A fall on a straight line (Brønsted line) without exception

$$\log (k_R/k_H)_A = a \cdot pK_a + B_A.$$

A more detailed analysis is needed for sets B and C. The five methyl pyridines which define set B can be divided into two subclasses (Fig. 2): Set B_1 contains 2-methyl, 2,4-dimethyl and 2,5-dimethylpyridines and set B_2 contains 2,3-dimethyl and 2,3,5-trimethylpyridines and is characterized by an interaction of two methyl groups in positions 2 and 3; these two subclasses can be plotted on two rather parallel lines with the same slope as in set A

$$\log (k_R/k_H)_{B1} = a \cdot pK_a + B_{B_1}$$

$$\log (k_R/k_H)_{B2} = a \cdot pK_a + B_{B_2}.$$

$B_A - B_{B_1}$ is the steric contribution of one-methyl group and has been used[9] to define the S° steric parameter for a methyl group. $B_{B_1} - B_{B_2}$ *is a measure of the extra steric requirement of a methyl group in the α-position when it is perturbed by another single methyl group in the β-position.*

For the six methylpyridines which compose set C, two of them, 2,6-dimethyl- and 2,4,6-trimethylpyridine, fall on a line parallel to set A, set B_1 and set B_2; this line defines set C_1

$$\log (k_R/k_H)_{C_1} = a \cdot pK_a + B_{C_1}.$$

$B_A - B_{C_1}$ is the steric contribution of two o,o'-methyl groups. All other pyridines from set C exhibit lower reactivity and for each example the vertical deviations from set C_1 is a measure of the extra steric retardation induced by the methyl groups interaction.

Thus the difference B_{C_1}–B_{C_2} results from the steric perturbation associated to the introduction of one methyl group in position 3 (2,3,6-trimethylpyridine **12**) whereas B_{C_1}–B_{C_3} is associated to the perturbation by two methyl groups in positions 3 and 4 (2,3,4,6-tetramethylpyridine **14**). The simultaneous perturbation of both o,o'-methyl groups by substitution in positions 3 and 5 is evidenced by the difference B_{c_1}–B_{C_4} and results in a net steric decrease of the rate as large as the one observed on going from unsubstituted pyridine to 2-methylpyridine. The effect of further substitution in position 4 (pentamethylpyridine **16**) is shown by the difference B_{C_5}–B_{C_4} (Fig. 2).

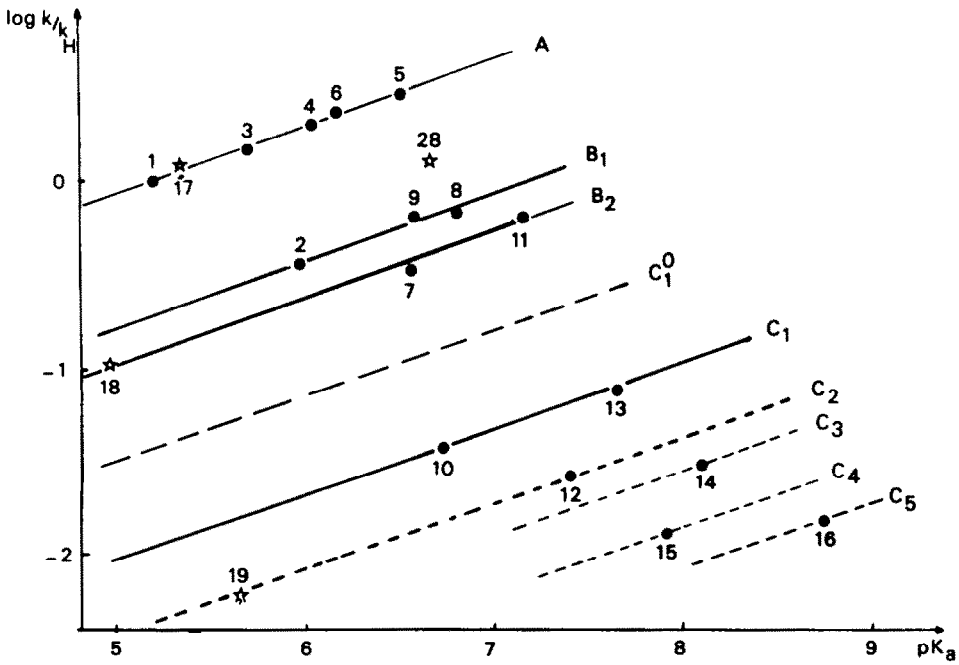


Fig. 2. Brønsted plot for the quaternization of polymethylpyridines. Definition of isosteric lines. Compounds **17**, **18** **19** are respectively isoquinoline, quinoline and 2-Me-quinoline. Compound **28** is 5,6,7,8-tetrahydroquinoline.

Table 2. Pure steric retardation parameters for structural blocks composed of several methyl groups (kinetic approach and treatment of the data according to Fig. 2 and Ref. 9)

	2-Me	2,3-DiMe	2,6-DiMe	2,3,6-TriMe	2,3,4,6-TetraMe	2,3,5,6-TMe	PentaMe
S^0	-0.73	-0.93	-1.95	-2.37	-2.53	-2.85	-3.08

More generally, deviations from the different classes could be used, if necessary, for the definition of new steric parameters for structural blocks consisting of several methyl groups in interaction.

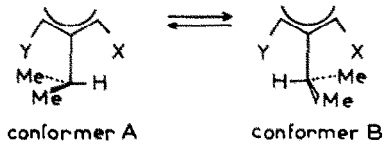
All extra steric retardations are given in Table 2.

We are aware that our set of data could appear not large enough to demonstrate on a statistical basis that lines B_1, B_2 and C_1 are strictly linear and strictly parallel to line A. The data at 25° results from 5 to 9 precise determinations at various temperatures. Further experimental points which would extend the pKa range by the introduction of functional groups in 4-position would be needed for an unquestionable demonstration of these points. However, within the range of variation we have, the assumption of parallel lines fits with the experimental data within the experimental error. A more serious limitation would have been a "clustering" effect of methyl derivatives on the definition of the slope of the reference line A. The Brønsted coefficient found in our study, 0.36 is quite similar to the one published recently for the alkylation of pyridines with methyl iodide[9] or ethyl iodide[24] in acetone on a far larger pKa and reactivity range. Thus we can assume that the isosteric lines A, B_1, B_2 and C_1 should be valid for functional pyridines which are not described in this paper. Set B_1 would correlate all 2-methylpyridines with positions 3 and 6 free. Set B_2 would correlate 2,3-dimethylpyridines with positions 4 and 6 free. Set C_1 would correlate 2,6-dimethyl-4-substituted pyridines.[25]

In summary, it appears that whenever a methyl group is perturbed by substitution in the *ortho* position, the reactivity is decreased as exemplified by comparison of line B_2 *vs* B_1, C_2 *vs* C_1 and C_4 *vs* C_1. *It can then be inferred from the kinetic approach that the perturbation of a methyl group results in an increase of its apparent size.* In a classical approach, this effect can be considered as a positive buttressing effect since the more buttressed the *ortho*-methyl group, the lower the reactivity. The next section will show that the situation is actually less simple than that.

(b) *Steric requirement of methyl groups from the conformational approach*

Barriers to rotation around single bonds and conformational state determinations are also classical ways to obtain information about the relative sizes of groups.[17] One of the main advantages of intramolecular processes around single bonds is the absence of electronic contribution. When an isopropyl group is attached to a sp^2 framework between two flanking o,o'-substituents, the bulky face[12] composed of the two methyl groups will be as far as possible from the more bulky flanking substituent, leading to a conformational preference which can be used to ascertain the relative size of the X and Y groups. *Thus when the steric size of X is larger than the steric size of Y conformer A will be more populated than conformer B.* We have therefore a very handy and precise tool for measuring the relative sizes of groups.



conformer A conformer B

Scheme 2.

When X and Y are both methyl groups, perturbation of these groups by other methyls should then affect both ground state conformations and barriers to rotation.

1-Isopropyl-2,6-dimethyl pyridinium perchlorates and 3-isopropyl-2,4-dimethylpyridine derivatives have been specially designed as material for such a study. Each of the o,o'-methyl substituents can be perturbed by the sequential introduction of extra methyl groups leading to the eight compounds listed in Figs. 3 and 4. All these compounds were prepared by treatment of the corresponding pyrylium salts with either isopropylamine (which is the only alternative for the preparation of the 1-iPr derivatives) or aqueous ammonia (see Experimental).

Barriers to rotation fall into the range of energy which allows the use of dynamic NMR techniques. On cooling, two conformers are observed in a range of temperatures easily accessible, 10 to −80°. The chemical shift assignments at low temperature for both series are given in Fig. 3. Unambiguous attributions are greatly facilitated by the presence of the nitrogen atom which induces useful shift differences between methyl groups in posiltions 2, 3 or 4 on the pyridine ring. A methyl group which undergoes the through space effect of the two methyls of the isopropyl (such as X in conformer B) appears at lower field than in the opposite conformational situation, as already exemplified in benzene,[26] thiazole[11a,b,27] and (thio)amide[11c,28] derivatives. This deshielding effect results[29] from the Buckingham contribution on the chemical shift which overbalances the Apsimon anisotropy contribution (shielding effect);[30] interestingly enough the methyl groups in the β-position appear upfield, probably from the preeminence of the Apsimon contribution compared to the Buckingham one in this remote geometrical situation.

We obtained the populations in the slow exchange region by curve fitting or by weighing the relative areas of the NMR signals. No dramatic changes were observed over a large range of temperatures for the populations. Barriers to rotation were provided (see experimental part) by lineshape analysis at least at three different temperatures in the exchange region on all exploitable signals.

The barriers to rotation and the populations are reported in Fig. 4.

The two first entries in Fig. 4 deserve some comments: The barrier is *ca* 4 kcal/mol lower in the 3-isopropylpyridines and -pyridinium salts than in the 1-isopropyl pyridinium salts. This is well accounted for by the drastic

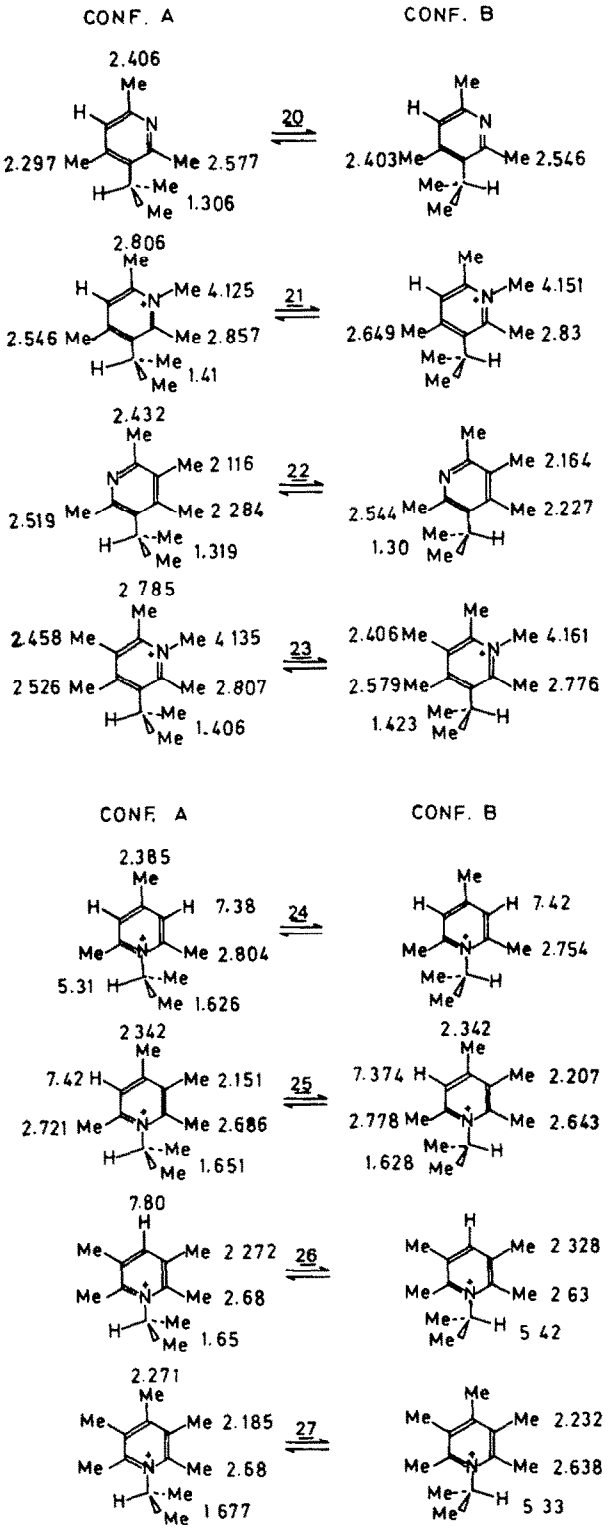


Fig. 3. Conformers and chemical shift assignments in the slow exchange region for 1-iPr-pyridinium perchlorates (solvent acetonitrile + ε-pentadeuteropyridine), 3-iPr-pyridines (solvent $CHFCl_2$), and 1-Me-3-iPr pyridinium iodides (solvent $CHFCl_2$).

changes on going from a single C–C bond to a single $\overset{+}{N}$–C bond together with the changes in the intracyclic N–C bond, which stiffens the interaction in the 1-isopropyl-pyridinium salt.[31]

Two remarkable features are seen when one increases the substitution on the cycle and thus the number of interacting methyl groups: (a) the barriers *decrease* in both series on going from the trimethyl-substituted compound to the pentasubstituted one; (b) the dissymmetric perturbation of one of the two α-methyl groups

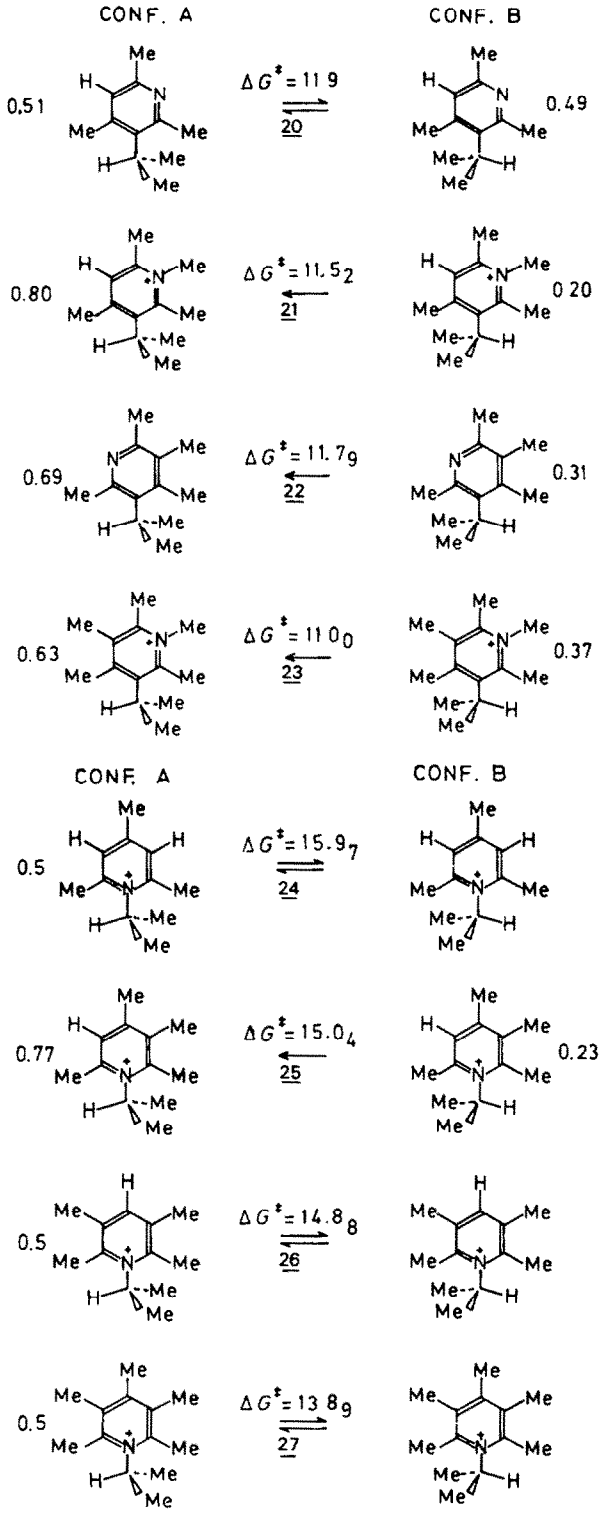
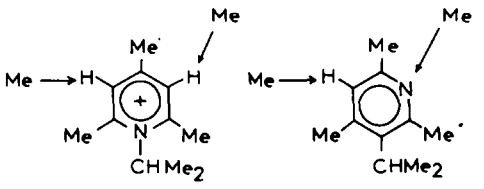


Fig. 4. Barriers to rotation (kcal/mol ± 0.1 kcal/mol) and populations for iPr-pyridine derivatives.

increases the population of the conformers in which the bulky face of the isopropyl group is directed towards the perturbed methyl group.

If one applies strictly the general rules for the conformational analysis of isopropyl systems, one might think that the apparent size of the o-methyl group is smaller under perturbation (negative buttressing effect) than in the unperturbed case.

In summary, at the end of this descriptive part, it turns out that the same perturbation on a similar framework (interaction of several methyl groups) leads to an *increase* of the "size" of the methyl group if kinetics of quater-



Scheme 3.

nization are considered, and to a *decrease* of the "size" if conformational states and barriers to rotation are considered.

DISCUSSION

There is no doubt that a methyl group is a three-pronged substituent but the fundamental question is to prove experimentally that this polyhedral shape has some noticeable effect on reactivity which cannot be accounted for by considering a methyl group as a spherical substituent. One has to ask if the apparent contradiction of the experimental facts can be accounted for by a spherical behaviour of the methyl group or if the conformational aspect has to be involved in order to get a consistent interpretation, with or without gear effect.

Kinetic approach

If one takes the set B_1 as a standard for the interaction of one methyl group on the substrate (2-methyl) and the incoming methyl group in the transition state, this structural block can be perturbed in two different ways by an extra methyl group.

Perturbation can occur in the position 3 (the so-called buttressing effect) or in position 6 (the so-called o,o'-effect). These two perturbations cannot be compared directly since the o,o'-effect combines two components: the major contribution results from the fact that the incoming methyl group is faced with two methyl groups which were not in interaction in the starting material; a simple additivity rule defines a theoretical line C_1^0 (Fig. 2) which can be easily deduced from the variation from line A to line B_1. In fact the experimental line C_1 shows a lower reactivity than expected. The difference C_1–C_1^0, which is the experimental manifestation of the non-additivity of the o,o'-effect, can be taken in our opinion has the result of the extra steric perturbation by the 6-methyl group.

Such an analysis which identifies the non-additivity part of the o,o'-effect to a perturbing contribution implies that the additivity of steric effects in o,o'-conditions is impossible as soon as through-space interactions are concerned. When two methyl groups (or other groups) are in interaction, the minimization of the strain is obtained by angular deformation (bending contribution), by bond length changes (stretching contribution), and by rotation of the groups in order to minimize the van der Waals repulsions. This leads to a geometrical relationship between the interacting groups which is impossible to symmetrize in order to get additivity in o,o'-effects. The additivity would have been observed if the methyl groups were stiff balls hanging on stiff bonds which of course is an obsolete view of steric interactions.

However, the non-additivity will still be observed if methyl groups are considered as stiff balls hanging on normal bonds. The non-additivity has been long recognized and differences in the bending abilities advocated.[32]

In order to obtain a more precise approach to this problem, molecular mechanics calculations using Allinger's 1973 force field have been performed on the transition state of the reaction between methyl iodide and 2-methylpyridine, 2,6-dimethylpyridine and 2,3-dimethylpyridine respectively.[33] The pertinent angular changes are reported in Scheme 5.

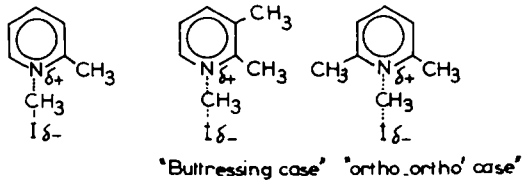
The initial β value was taken in all cases equal to 118.5°. Thus in the 2-methyl case, β increases from 118.5 to 120.8° ($\Delta\beta = 2.3°$), in the 2,6-dimethyl case the final value is 119.5° ($\Delta\beta = 1°$). On the other hand the angular change is larger in 2-methyl than in the 2,6-dimethyl case. These modifications in geometry point out clearly that additivity would have been fortuitious. In the 2,3-dimethyl case $\Delta\alpha = 4°$ whereas the angular change of the 2-methyl is small.

The experimental perturbing effect of the 3-methyl group is smaller ($\delta S° = -0.20$) than the perturbing effect of the 6-methyl group ($\delta S° = -1.95$-2 $(-0.73) = -0.49$; Table 2.) This could be related to the dissymmetry which is to be found in the reference structural block composed of one methyl group fixed on the molecule and a methyl group on a bond being formed.

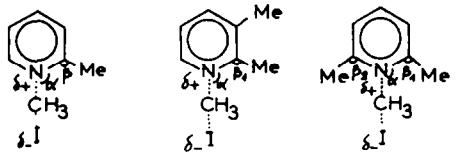
Summing up, all the quantitative data derived from the kinetic approach could be interpreted on the base of difference in bending abilities of spherical methyl groups with no reference to the polyhedral shape of the methyl groups.

Molecular mechanics calculations suggest that as soon as two methyl groups are in o,o-positions on a six-membered ring, the preferred conformation is a "gear-clashed one" in which two hydrogens are pointing apart of the structural block defined by the two methyl groups and stand into the plane of the sp^2 framework.[34] Thus the presence of the perturbation in position 3 induces a preferred conformational state for the methyl group in position 2 for which one hydrogen is placed in the plane of the ring and is pointing towards the reactive nitrogen as shown in Scheme 6. This is also shown in the symtetramethylpyridine case in which the double gear clashed conformation is far more populated than any other according to MMI calculations.

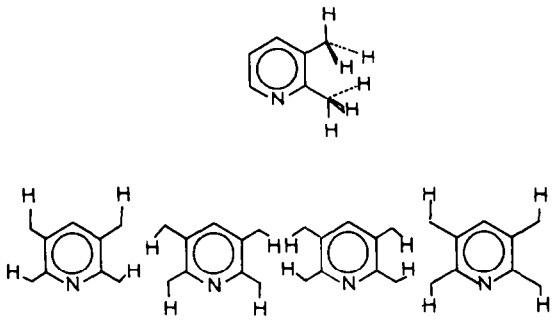
The question arises whether such an induced conformational state could account for the observed steric retardation. Coming back to the experimental evidences, we have to find model compounds in which the hydrogen is blocked into the plane and directed towards the reac-



Scheme 4.



Scheme 5.



Scheme 6.

tive nitrogen and model compounds in which two hydrogen atoms are locked in place straddling the plane and pointing toward the nitrogen: such models exist in the isoquinoline and quinoline series. Isoquinoline **17** should be a model for unsubstituted pyridine; quinoline **18** should be a model for the 2,3-dimethyl-pyridine and 2-methylquinoline **19** a model for the 2,3,6-trimethyl-pyridine. 5,6,7,8-Tetrahydroquinoline **28** will be a model for the straddling hydrogens (Scheme 7).

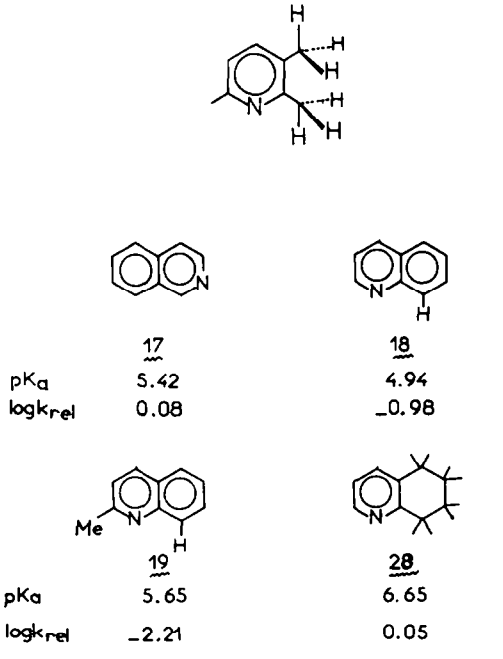
The relative rate constants of alkylation by methyl iodide have been determined for compounds **17–19** by Zoltewicz and Deady in DMSO some years ago.[35] The relative rate constant of alkylation by methyl iodide for **28** in acetonitrile has been published recently by Seeman *et al.*[19g] Their data are directly applicable, since the coefficients of the Brønsted equation are known in DMSO, acetonitrile, and acetone.[9]

Isoquinoline **17** falls on the A line (Fig. 2), quinoline **18** falls on the B_2 line and 3-methylquinoline **19** falls on the C_2 line.

Thus, it can be deduced that a perturbed methyl group has a similar steric behaviour as a benzo substituent in which the peri hydrogen is by nature pointing into the plane and directed towards the reactive nitrogen. We consider this similarity as an experimental evidence in favour of the conformational aspect of the steric effect of a methyl group.

It is clear that bending contributions are also involved as exemplified in the enhanced steric requirement in 2,3,4,6-tetramethylpyridine ($S^\circ = -2.53$). 5,6,7,8-Tetrahydroquinoline **28** ($\log k/k_H = 0.05$, pKa = 6.65)[19g] is too reactive to fall on the isosteric line B_1. This can be interpreted by assuming that two conformational states roughly equally populated exist for the methyl group already in the definition of line B_1. One in which the methyl group has one hydrogen in the plane and pointing toward the nitrogen and another in which the hydrogen is located into the plane but is pointing toward the hydrogen in position 3.

The extra steric retardation or the so-called positive buttressing effect of the methyl groups results primarily from an induced conformational state, whereas the other modes of strain minimization are also in operation. Thus the effective size of the methyl group is conformationally dependent but no reference to gear effect interpretation is needed.



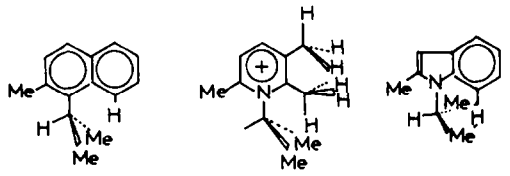
Scheme 7.

Conformational analysis approach

Barriers to rotation. The decrease of the barriers on going from the trimethyl-substituted derivatives to the pentasubstituted ones could arise from a better accommodation of the strain in the transition state than in the ground state. In the transition state, both methyl groups of the isopropyl are on the same side of the molecular plane and it follows that the van der Waals interactions are better accommodated through in and out of plane bending contributions than in the locked ground state. Examples in which the difference of accommodation of the strain between the ground state and the transition state results in lower barriers are known in ethane derivatives,[36] and in sulfonamide derivatives.[37] "Buttressing effect in the opposite direction" has been evidenced by Oki *et al.*[38] recently in the triptycene series and we have called attention to the erroneous results which can be derived from noncircumspect use of barriers to rotation for estimating the apparent spatial requirement of substituent when ground state strains are involved.[39]

Barriers to rotation do not shed light on the problem of the molecular shape of the methyl group but confirm that the total strain in the ground state is increased with polysubstitution.

Conformational preferences. The origin of the reverse conformational preference cannot be explained by the spherical shape of a methyl which prevents any negative buttressing effect. On the contrary, there are several indications that two o-methyl groups prefer a gear-clashed conformation in six-membered rings. (1) According to microwave spectroscopy of o-xylene the methyl groups both stagger the intervening C_{Ar}–C_{Ar} bond.[40] (2) As mentioned before, both CNDO/2[34] and molecular mechanics[45] calculations (Scheme 6) support the gear-clashed conformation. (3) The results of the kinetic experiments are perfectly understood with the assumption that a perturbed o-methyl group has a



Scheme 8.

hydrogen atom in the plane and pointing towards the nitrogen.

Furthermore, we have reason to believe that this pointing hydrogen is the source of the unexpected conformational preference of the isopropyl group in the perturbed systems. The driving force would be the nonoccurrence of the 1,6 frontal interaction of two hydrogens in the plane of the sp^2-hybridized framework in the preferred conformation. This assumption is supported by the following two experimental observations:

(i) The apparent order of sizes of alkyl group has been shown to be strongly perturbed as soon as locking on a pointing hydrogen is possible as in the case of 3,4-diisopropyl-5-methylthiazoline-2-thione in which an isopropyl group apparently had a smaller steric requirement than a methyl group.[11]

(ii) The isopropyl group is preferentially locked on the peri hydrogen in 1-isopropyl-2-methylnaphthalene[26] and in N-isopropyl-2-methylindole.[45]

Thus the polyhedral aspect of the molecular shape of the methyl group accounts for the reverse (apparent) conformational preference and the so-called negative buttressing effect. Obviously, this is a case of conformational transmission, which is caused by interaction between polyhedral methyl substituents and thus, according to our definition,[11b] a case of (static) gear effect.

CONCLUSION

It turns out that the same conformational explanation which involves the polyhedral shape of a methyl group accounts for the steric retardation in the quaternization kinetics and the conformational preference in isopropyl derivatives. In the kinetics, the perturbed methyl group adopts a conformation which hinders the nucleophilic center, whereas in the conformational analysis the same perturbed methyl group affords a locking point for the next polyhedral substituent. These arguments are supported in both cases by the comparison with the benzoanalogues (quinoline for quaternizations and naphthalene or indole for conformational preference).

The positive buttressing effect (kinetic approach) rests mainly on an induced conformational state which involves the polyhedral shape of the methyl group, with no necessary gear effect. The negative buttressing effect is a case of conformational transmission between polyhedral substituents in close contact (gear effect).

EXPERIMENTAL

(a) *Compounds for study*

Mono-, di- and tri-substituted pyridines are commercially available. 2,3,4,6-Tetramethyl, 2,3,5,6-tetramethyl and pentamethyl-pyridines were prepared from the corresponding pyrylium salts as already described.[21,41] Pure samples were obtained by careful distillation followed by preparative gas chromatography on a 3.5 m × 1/4 in e.d. stainless steel column packed with Chromosorb PAW 80/100, 5% KOH, 20% Apiezon L.

3-*Isopropyl*-2,4,6-*trimethylpyridine* **20** was obtained by diacylation of 2,4-dimethylpentan-2-ol by Ac_2O in $HClO_4$ (70%) followed by treatment with aqueous ammonia.[42] Pure compound was obtained as colourless oil by preparative GLC: ^1H NMR ($CDCl_3$) δ 1.31 (6H, d), 2.32 (3H, s, 4-Me), 2.42 (3H, s, 6-Me), 2.58 (3H, s, 2-Me), 3.37 (1H, septet), 6.78 (1H, s, 5-H); mass spectrum (70 eV) *m/e* (rel int) 163 (39.4), 148 (100), 146 (6.5).

3-*Isopropyl*-1,2,4,6-*tetramethylpyridine iodide* **21** was prepared from 3-isopropyl-2,4,6-trimethylpyridine quaternization by methyl iodide in dry acetone in a NMR tube followed by the replacement of the excess of methyl iodide and acetone by $CHFCl_2$ and TMS on the vacuum line before the usual procedure of NMR sample preparation.[11c]

3-*Isopropyl*-2,4,5,6-*tetramethylpyridine* **22** was obtained by diacylation of 3,5-dimethylhexan-3-ol by Ac_2O in $HClO_4$ (70%) followed by treatment with aqueous ammonia.[42] Pure compound was obtained as colourless oil by preparative GLC: ^1H NMR ($CDCl_3$) δ 1.29 (6H, d), 2.16 (3H, s, 5-Me), 2.27 (3H, s, 4-Me), 2.45 (3H, s, 6-Me), 2.54 (3H, s, 2-Me), 3.34 (1H, septet; mass spectrum (70 eV) *m/e* (rel int) 177 (31), 163 (14.3), 162 (100), 91 (6.1), 41 (11.3), 39 (6.4).

3-*Isopropyl*-1,2,4,5,6-*pentamethylpyridinium iodide* **23** was prepared by the same procedure as 3-isopropyl-1,2,4,6-tetramethylpyridinium iodide.

1-*Isopropyl*-2,3,5,6-*tetramethylpyridinium perchlorate* **26**. 2-Pentanol (1 mol) was diacetylated[21,47] with acetic anhydride (5 mol) and 70% perchloric acid (1 mol) affording a 4:1 mixture of 2,3,5,6-tetramethylpyrylium and 3-ethyl-2,6-dimethylpyrylium perchlorates. After completion of the reaction, ethyl ether was added and the lower layer of perchlorates was separated, washed with two portions of ethyl ether, and then added dropwise into an excess of ethanolic isopropylamine with cooling. After 1 h at room temp. ethyl ether was added until the cloudiness persisted, and the mixture was left overnight in the refrigerator. The product (white needles) was filtered off and recrystallized from ethanol-ethyl ether. M.p. 168°. Anal C, H, N. ^1H NMR (F_3CCOOH): δ = 1.92 (d, 6H, iPr-Me_2, J = 7.5 Hz), 2.58 (s, 6H, β-Me_2), 2.98 (6H, s, α-Me_2), 5.81 (1H, septet, iPr-CH, J = 7.5 Hz), 8.18 (1H, s, γ-H).

1-*Isopropyl*-2,3,4,6-*tetramethylpyridinium perchlorate* **25**. 2,3,4,6-Tetramethylpyrylium perchlorate[48] (56 mmol) was treated with 168 mmol isopropylamine in 20 ml ethanol. Similar work-up as above afforded needles with m.p. 144–145° in 72% yield. Anal C, H, N. ^1H NMR (F_3CCOOH): δ = 1.80 (6H, d, iPr-Me_2, J = 7 Hz), 2.39 (3H, s, β-Me), 2.52 (3H, s, γ-Me), 2.87 (6H, s, α-Me_2), 5.44 (1H, septet, iPr-CH, J = 7 Hz), 7.40 (1H, s, β-H).

1-*Isopropyl*-2,3,4,5,6-*pentamethylpyridinium perchlorate* **27**. Diacetylation[41] of 3-methyl-3-pentanol (1 mol) with Ac_2O (5 mol) and 70% perchloric acid (1 mol) yielded a 3:1 mixture of pentamethylpyrylium and 4-ethyl-2,3,6-trimethylpyrylium perchlorates. After extraction with ether, the lower pyrylium salt layer was treated with excess ethanolic isopropylamine and worked up as described above. After two recrystallizations from ethanol-ethyl ether, the pyridinium salt with symmetrical structure had m.p. 157°. Anal C, H. N. ^1H NMR (F_3CCOOH): δ = 1.87 (6H, d, iPr-Me_2, J = 7 Hz), 2.50 (6H, s, β-Me_2), 2.57 (3H, s, γ-Me), 2.92 (6H, s, α-Me_2), 5.58 (1H, septet, iPr-CH, J = 7 Hz).

1-*Isopropyl*-2,4,6-*trimethylpyridinium perchlorate* **24**. 2,3,6-Trimethylpyrylium perchlorate[46] (50 mmol) was added to a solution of 0.1 mol isopropylamine in 20 ml ethanol. After 1 hr at room temp. ethyl ether was added until a cloudy solution resulted. The product recrystallized overnight in the cooler, was filtered off, washed with ethyl ether, and recrystallized from ethanol-ethyl ether. Yield 75%, m.p. 171-172°. Anal C, H, N. ^1H NMR (F_3CCOOH): δ = 1.78 (6H, d, iPr-Me_2, J = 7 Hz), 2.52 (3H, s, γ-Me), 2.91 (6H, s, broad at room temp., α-Me_2), 5.45 (1H, septet, iPr-CH, J = 7 Hz), 7.47 (2H, s, β-H_2).

(b) *Kinetics studies by conductometry and dynamic nuclear magnetic resonance*

Performed according to Refs. 21, 43 and 11c, respectively. Selected data for DNMR are given in Tables 3 and 4.

(c) *Molecular mechanics calculations*

Performed using the MMI program developed by Allinger *et al.* employing their 1973 force-field.[44] Since this force-field is not parameterized for the pyridine system the ring skeleton was kept rigid and idealized geometries were used.[33]

Table 3. Temperature ranges for lineshape analysis and conformer population data for 20–27

Cpds	Solvent	Temp. (°C)[c]	Temp. range (°C)[d]	Signals[d]	nb[e]
20	a	-95	-48 → -42	2-Me, 4-Me	6
21	a	-93	-58 → -48	4-Me	4
22	a	-93	-60 → -53	4-Me, 5-Me	6
23	a	-90	-68 → -64	4-Me, 5-Me	7
24	b	-20	+15 → +30	2,6-Me	6
25	b	-31	-13 → 0	3-Me	4
26	b	-30	-5 → +10	2,6-Me and 3,5-Me	8
27	b	-36	-23 → -2	2,6-Me and 3,5-Me	10

[a] $CHFCl_2$. [b] CD_3CN, ε-C_5D_5N. [c] Slow exchange region for the integration.

[d] Exchange region used for lineshape analysis. [e] Number of lineshape analysis.

Table 4. Selected examples of lineshape analysis data (two sites)

Cpds	Temp.	p_B	T_{2A}	T_{2B}	$\Delta\nu$ (Hz)	τ_B	ΔG^* (temp.)
20	-48.2	0.49	0.15	0.15	10.56	0.090	11.88
21	-48.7	0.20	0.14	0.14	10.24	0.035	11.5
22	-59.5	0.31	0.14	0.14	4.84	0.3	11.79
23	-68.3	0.37	0.19	0.19	5.36	0.14	10.99
24	+26.0	0.50	0.23	0.17	5.0	0.08	15.95
25	-0.3	0.23	0.14	0.14	4.40	0.2	15.0
26	-4.7	0.50	0.17	0.16	5.60	0.26	14.88
27	-19.9	0.50	0.24	0.24	4.10	0.20	13.88

Apart from this restriction full relaxation was allowed. Force constants not accessible in the program were estimated for the purpose of this investigation.[33] That the essence of the results are not artefacts due to the constraints in the calculations was shown by calculations on analogous benzene derivatives for which full relaxation including a well-defined force-field was allowed.[45]

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