Deuterium kinetic isotope effects in the quaternization of polymethylpyridines (CH3 or CD3) with methyl iodide or D3-methyl iodide

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Deuterium Kinetic Isotope Effects in the Quaternization of Polymethylpyridines (CH_3 or CD_3) with Methyl Iodide or [$^2H_3$]Methyl Iodide

J. Chem. Research (S), 1982, 44–45
J. Chem. Research (M), 1982, 0559–0583

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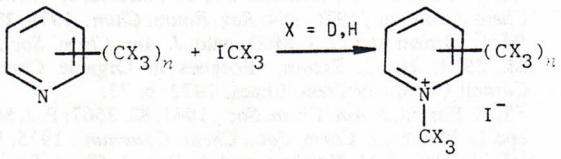
The rates of quaternization of six CH_3- or CD_3-substituted pyridines in acetone at 25 °C with CH_3I or CD_3I were determined conductimetrically. The main



results, presented in Table 1, indicate that in all cases replacement of CH_3 by CD_3 causes a small acceleration. This secondary isotope effect could be due to steric and/or electronic components. Indeed, it is known that deuterium has a smaller volume,[7,8,10] and is an electron donor,[12–14] relative to protium. An estimation based on the Brönsted relationship shows that the three accelerating secondary isotope effects obtained on replacing two α-CH_3 groups by CD_3 groups in the pyridines shown in Table 3 consist approximately of equal amounts of steric and electronic (inductive) components. On the other hand, for pyridines which do not have two α-methyl groups, replacement of CH_3 by CD_3 gives a secondary isotope effect for which no steric component can be detected and all the acceleration is apparently caused by an inductive effect (*i.e.* the Brönsted relationship accounts for the whole acceleration due to an increase in the pK_a of the pyridine on deuteriation).

An acceleration is also observed on deuteriation of the alkyl halide. In this case, however, the dissection into steric and electronic components is no longer possible.

Pentamethylpyridine and its deuteriated congener show different behaviour from all the other pyridines which upsets the precision of the kinetic data: it does not show clean second-order kinetics, the initially steep variation becoming linear only after *ca.* 0.2% of the

Table 3 Steric and inductive (electronic) components of the secondary isotope effects in the quaternization of CH_3/CD_3- or H/D-substituted pyridines

		Secondary isotope effect (%)			
Halide	Pyridine	Total	Inductive	Steric	Ref.
CH_3I	2,3,5,6-Me_4	11.0	4.9	6.1	a
CD_3I	2,3,5,6-Me_4	8.5	4.9	3.6	a
CD_3I	2,3,4,5,6-Me_5	17.5	7.9	9.6	a
CH_3I	2-Me	3.0	2.3	0.7	8
CH_3I	2,6-Me_2	9.5	4.9	4.6	8
CH_3I	pyridine	3.1	—	−1.4	13
CH_3I	[4-^{2}H]pyridine	1.2	—	—	13

[a]Present work; maximum error 3% for the first two entries and 5% for the last.

Table 1 Kinetic data and pK_a values for reactions in acetone at 25 ± 0.1 °C

Compound	pK_a[a]	10^6k/l mol^{-1} s^{-1}	k_{rel}	log k_{rel}
A. Quaternization with CH_3I				
Pyridine (py)	5.19	229[b]	1	0
3,5-$(CH_3)_2$-py	6.15	521	2.28	0.36
2,4,6-$(CD_3)_3$-py	7.50[c]	12.6	0.055	−1.26
2,3,5,6-$(CH_3)_4$-py	7.91	2.92	0.013	−1.89
2,6-$(CD_3)_2$-3,5-$(CH_3)_2$-py	7.96[c]	3.24	0.014	−1.85
2,3,4,5,6-$(CH_3)_5$-py	8.75	3.5[d]	0.015	−1.82
2,4,6-$(CD_3)_3$-3,5-$(CH_3)_2$-py	8.83[c]	5.23[e]	—	—
B. Quaternization with CD_3I				
3,5$(CH_3)_2$-py	6.15	597	2.61	0.42
2,3,5,6-$(CH_3)_2$-py	7.91	3.31	0.014	−1.84
2,6-$(CD_3)_2$-3,5-$(CH_3)_2$-py	7.96[c]	3.59	0.016	−1.80
2,3,4,5,6-$(CH_3)_5$-py	8.75	4.0[d]	0.017	−1.76
2,4,6-$(CD_3)_3$-3,5-$(CH_3)_2$-py	8.83[c]	4.7[d]	0.021	−1.69

[a]Refs. 14 and 19. [b]C. Roussel, unpublished work. [c]Data corrected by constant increment, *cf.* ref. 14. [d]Obtained by graphical extrapolation at 298 K. [e]Value at 302.9 K.

*To receive any correspondence.

pyridine has reacted. The rates given in Table 1 were thus determined by extrapolation from the linear portion.

It was verified that this particular effect is not due to traces of water, pentamethylpyridine being the only compound which is very hygroscopic and affords a crystalline hemihydrate. The only plausible explanation is the presence of a small amount (0.1–0.5%) of the valence isomers pentamethyl-Dewar-pyridine or azaprismane which should be much more nucleophilic than the aromatic congener. It is known that such valence isomers are stabilized by steric factors such as the large degree of substitution present in pentamethylpyridine.[31] To check this hypothesis, the kinetics of four quaternizations with methyl iodide were studied under comparable conditions: 2,3,5,6-tetramethyl- and 2,3,4,5,6-pentamethyl-pyridines both before and after u.v. irradiation at −80 °C. Only the irradiated pentamethylpyridine shows a marked deviation, in keeping with the assumption that u.v. irradiation increases the low proportion of the reactive valence isomers.

The deuteriated pyridines listed in the Table and their non-deuteriated congeners were prepared from the corresponding pyrylium salts, synthesized by diacetylation of alkenes.[34,35] Refluxing methyl-substituted pyrylium salts in deuterium oxide allows a rapid deuteriation of γ- and (more slowly) of α-methyl groups.[3–5] Subsequent reactions with aqueous ammonia yield pyridines.[34–36]

Techniques used: Conductimetry, ^{1}H n.m.r.

References: 37

Table 2: Logarithms of relative quaternization rate constants for polymethylpyridines

Table 4: Isotopic effects in the quaternization of the same substrate with CD_3I or CH_3I, expressed by $100(k_D/k_H - 1)\%$

Figure 1: Deuteriation and de-deuteriation of γ- and α-methyl groups in pyrylium salts by heating in D_2O and H_2O respectively

Figure 2: Dissection of total isotope effect (represented in a Brönsted diagram) into a steric and an electronic component

Figure 3: Quaternization of polymethylpyridines in acetone (at 25 °C) by methyl iodide: anomalous behaviour of pentamethylpyridine

Paper: E/151/81 Received: 2nd September 1981

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[5]E. Gard, A. Vasilescu, I. I. Stanoiu, F. Chiraleu, and A. T. Balaban, *Rev. Roum. Chim.*, 1973, **18**, 257.
[7]A. T. Balaban, I. I. Stanoiu, and F. Chiraleu, *J. Chem. Soc., Chem. Commun.*, 1976, 984; *Rev. Roum. Chim.*, 1978, **23**, 187.
[8]H. C. Brown and G. J. McDonald, *J. Am. Chem. Soc.*, 1966, **88**, 2514; H. C. Brown, 'Boranes in Organic Chemistry,' Cornell University Press, Ithaca, 1972, p. 73.
[10]L. S. Bartell, *J. Am. Chem. Soc.*, 1961, **83**, 3567; P. J. Mitchell and L. Phillips, *J. Chem. Soc., Chem. Commun.*, 1975, 908.
[12]E. A. Halevi, M. Nussium, and A. Ron, *J. Chem. Soc.*, 1963, 866.
[13]B. D. Batts and E. Spinner, *J. Chem. Soc.*, 1968, 789.
[14]A. T. Balaban, I. I. Stanoiu, and E. Gard, *Rev. Roum. Chim.*, 1977, **22**, 1191.
[19]D. D. Perrin, 'Dissociation Constants of Organic Bases in Aqueous Solution,' Butterworths, London, 1965.
[31]R. D. Chambers and R. Middleton, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1500.
[34]H. G. Rajoharison, C. Roussel, and J. Metzger, *J. Chem. Research*, 1981, *(S)* 186; *(M)* 2157.
[35]A. T. Balaban, A. Bota, F. Chiraleu, E. Sliam, A. Hanes, and C. Draghici, *Rev. Roum. Chim.*, 1977, **22**, 1003.
[36]H. G. Rajoharison, H. Soltani, M. Arnaud, C. Roussel, and J. Metzger, *Synth. Commun.*, 1980, **10**, 195; M. Arnaud, A. Pedra, C. Roussel, and J. Metzger, *J. Org. Chem.*, 1979, **44**, 2979.

J.Chem.Research (M), 1982, 0559-0583

Paper E/151/81 Received 2nd September 1981

Deuterium Kinetic Isotope Effects in Quaternization of Polymethylpyridines (CH_3 or CD_3) with Methyl Iodide or ($^2H_3$) Methyl Iodide.

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The rates of quaternization of six CH_3- or CD_3- substituted pyridines with CH_3I or CD_3I were determined conductimetrically. The accelerations observed on replacing two α-CH_3 by α-CD_3 groups are due both to steric and electronic factors in approximately equal amounts. The smaller accelerations observed on replacing one α-CH_3 by a CD_3 group (H.C. Brown's data) or pyridine hydrogens by deuterium (Batts and Spinner's data) seem to be mostly due to electronic factors. The accelerations observed on replacing CH_3I by CD_3I cannot be dissected into steric and electronic components. The anomalous initial kinetic behaviour of pentamethylpyridine indicates that it probably contains a small amount (0.1 - 0.5 %) of its valence isomer which, being more basic, reacts faster ; prior UV irradiation does indeed enhance this effect on the kinetics.

1) Introduction

The present investigation emerged from two convergent research directions pursued at Bucharest (i) and Marseilles (ii), respectively.

(i) Pyrylium salts [1,2] were shown[3] to undergo deuterium exchange at α- and γ-standing 'benzylic' positions of alkyl side-chains on heating in deuterium oxide. The rate of deuteriation is about ten times higher [4,5] in γ than in α owing to the lower energy of the γ- anhydrobase (alkylidenepyran) relative to the α- anhydrobase.[6] This observation allowed the preparation of the selectively-deuteriated pyridines used in this study by reactions such as those depicted in Figure 1, followed by conversion of the respective pyrylium salts into pyridines by treatment with ammonia.

It was observed that the α-deuteriated pyridines presented a

[1]A.T. Balaban, W. Schroth and G. Fisher, Adv. Heterocyclic Chem. 10, 241 (1969).

[2]A.T. Balaban, in New trends in Heterocyclic Chemistry, (eds. R.B. Mitra et al.), Elsevier, Amsterdam, p 79 (1979).

[3]A.T. Balaban, E. Gard, A. Vasilescu and A. Barabas, J. Labelled Comp. 1, 266 (1965).

[4]E. Gard, A. Vasilescu, G.D. Mateescu and A.T. Balaban, J. Labelled Comp., 3, 196 (1967).

[5]E. Gard, A. Vasilescu, I. I. Stanoiu, F. Chiraleu, and A.T. Balaban, Rev. Roumaine Chim., 18, 257 (1973).

[6]G.V. Boyd, Rev. Roumaine Chim., 12, 1133 (1967).

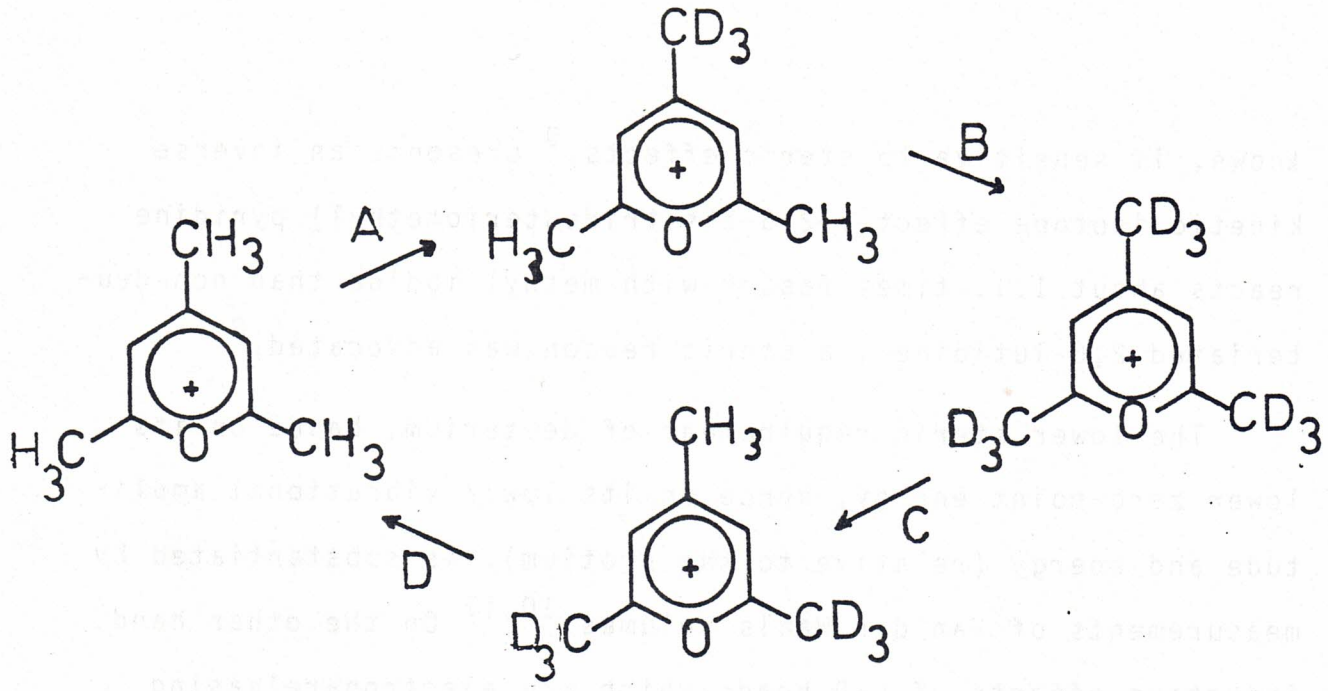

Figure 1: Deuteriation and de-deuteriation of α- and γ- methyl groups in pyrylium salts by heating in D_2O and H_2O respectively. A: D_2O, 80°, 10 min.; B: D_2O, 100°, 1 hr.; C: H_2O, 80°, 20 min.; D: H_2O, 100°, 2 hrs.

higher induced shift than the non-deuteriated counterparts in the presence of europium-containing lanthanide shift reagents.[7] This finding is in agreement with the smaller effective volume of a CD_3 than of a CH_3 group (indeed, the frequency and amplitude of vibrations are lower for the heavier isotope).

Brown and McDonald [8] reported that the quaternization which, as

[7] A. T. Balaban, I. I. Stanoiu, and F. Chiraleu, Chem. Commun., 984 (1976); Rev. Roumaine Chim., 23, 187 (1978).

[8] H. C. Brown and G. J. McDonald, J. Amer. Chem. Soc., 88, 2514 (1966); H. C. Brown, 'Boranes in Organic Chemistry', Cornell University Press, Ithaca, N. Y., 1972 p. 73.

known, is sensitive to steric effects,[9] presents an inverse kinetic isotope effect : 2,6-bis(trideuteriomethyl) pyridine reacts about 1.1. times faster with methyl iodide than non-deuteriated 2,6-lutidine ; a steric reason was advocated.[8]

The lower steric requirement of deuterium, based on its lower zero-point energy, hence on its lower vibrational amplitude and energy (relative to the protium), is substantiated by measurements of Van der Waals volumes.[10,11] On the other hand, inductive effects of C-D bonds which are electron-releasing relative to C-H bonds [12] were shown to increase the basicity of ($^2H_5$) pyridine by Batts and Spinner, [13] and the basicity of selectively methyl- deuteriated 2,4,6-triméthylpyridine by Balaban et al.[14]

Since the secondary isotope effect is a negative one, it shall be expressed by k_D/k_H instead of the usual expression k_H/k_D.

(ii) On the other hand, the steric effect of alkyl substituents was investigated with various heterocyclic models

[8] H. C. Brown and G. J. McDonald, J. Amer. Chem. Soc., 88, 2154 (1966).

[9] J. A. Zoltewicz and L. W. Deady, Adv. Heterocyclic Chem., 22, 71 (1978).

[10] L. S. Bartell, J. Amer. Chem. Soc., 83, 3567 (1961).
P. J. Mitchell and L. Phillips, Chem. Commun., 908 (1975).

[11] K. Clusius and K. Weigand, Z. Physik. Chem., B46, 1 (1940).

[12] E. A. Halevi, M. Nussium and A. Ron, J. Chem. Soc., 866 (1963).
E. A. Halevi, Prog. Phys. Org. Chem., 1, 109 (1963).

[13] B. D. Batts and E. Spinner, J. Chem. Soc., 789 (1968).

[14] A. T. Balaban, I. I. Stanoiu and E. Gard, Rev. Roumaine Chim.,22, 1191 (1977).

including pyridine : these studies on steric effects concern intermolecular as well as intramolecular effects ; they were performed by kinetic studies in the former case [15,16] or by dynamic nuclear magnetic resonance in the latter.[17]

Based on these two converging research directions, it was decided therefore to investigate the quaternization rates of CH_3- and CD_3 - substitued pyridines with CH_3I or CD_3I, and try to dissect any isotope effects into electronic and steric components.

[15] R. Gallo, M. Chanon, H. Lund and J. Metzger, Tetrahedron Letters, 3857 (1972).
U. Berg, R. Gallo, J. Metzger and M. Chanon, J. Amer. Chem. Soc., 98, 1260 (1976). U. Berg, R. Gallo, G. Klatte and J. Metzger, J. Chem. Soc. Perkin II 1350 (1980).

[16] C. Roussel, R. Gallo, M. Chanon, and J. Metzger, J. Chem. Soc. Perkin II 1304 (1974).

[17] C. Roussel, A. Liden, M. Chanon, J. Metzger, and J. Sandström, J. Amer. Chem. Soc., 98, 2847 (1976).
U. Berg and C. Roussel, J. Amer. Chem. Soc., 102, 7848 (1980).
C. Roussel, R. Gallo, J. Metzger and J. Sandström, Org. Magn. Res. 14, 120 (1980).
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2- Results

The relative rates of quaternization have to be measured with a high precision in order to determine the isotope effects. We selected the conductimetric method which presents relative to other methods (titration of the iodine anion, NMR competition)[9] the following advantages : it requires small amounts of reagents and it gives reliable kinetic constants at low conversions (up to 1 %). [18] (See experimental part)

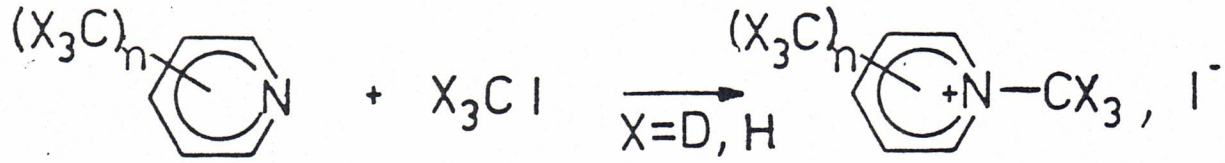
For pyridines with low reactivity this method is the only alternative. The precision of the conductimetric method is comparable to that of the titration. However, in order to obtain the best performance, the conductimetric method requires time-consuming calibrations, very pure reagents and solvents, and a rigourously constant temperature.

Kinetic measurements were effected in acetone at 25° C and initial rate constants were obtained by least squares calculations in all cases except for pentamethylpyridine with does not present clean kinetics with a constant k_2 value at the very begining of the reaction (i.e. at conversions up to 0.5 % ; see section 5 below). In this case, the measurements were performed at four temperatures in the range 283-303 K and in each case the rate constant was determined graphically from the final linear portion.

The quaternization with methyl iodide 2 of various methyl-substituted pyridines 1 (the Menschutkin reaction) has second order kinetics.[9]

[9] J.A. Zoltewicz and L. W. Deady, Adv. Heterocyclic Chem., 22, 71 (1978).

[18] R. Gallo, Thesis University of Marseilles 1971.



Independent modification of the concentrations of 1 and 2 leads to the same value for k_2 at constant temperature $T = 298^{o}K$ within the error limits(see experimental part).

The results are presented in Table 1 together with the pK_a values. It was determined earlier by measuring relative pK_a values of selectively-deuteriated 2,4,6-trimethylpyridines[14] that each replacement of an α- or γ-standing CH_3 by a CD_3 group increases the pK_a of sym-collidine by ca 0.025. The pK_a values are taken from reference 19.+

The same log k_{rel} values are rearranged in a different form in Table 2 to evidence more clearly the isotopic effect.

+ A referee pointed out rightly that the observed difference in pKa values could also result from steric changes going from CH_3 to CD_3. The additivity of the pKa values in simple pyridines : pyridine 5.19, 2-Me-pyridine 5-96 and 2,6-diMepyridine 6.72, is a strong argument against any participation of the steric effect as long as small changes are involved which is obviously the case in deuterium-hydrogen exchanges.
However it is well known that larger steric changes (i.e. Me → tBu) could lead to both electronic and steric contributions in the observed pKa changes.

[14] A. T. Balaban, I. I. Stanoiu and E. Gard, Rev. Roumaine Chim. 22, 1191 (1977).

[19] D. D. Perrin, ' Dissociation Constants of Organic Bases in Aqueous Solution', Butterworths, London 1965. cf. also A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases: a laboratory Manual", Methuen London, 1962.

Table 1 : Kinetic data (k values, l $mol^{-1} sec^{-1}$) and pK_a values, in acetone at 25 ± 0.1° C.

Compound	pK_a [a]	k (10^{-6})	k_{rel}	log k_{rel}
A. Quaternization with methyl iodide (CH_3I)				
Pyridine	5.19	229 [b]	1	0
3,5-$(CH_3)_2$	6.15	521	2.28	0.36
2,4,6-$(CD_3)_3$	7.50 [c]	12.6	0.055	-1.26
2,3,5,6-$(CH_3)_4$	7.91	2.92	0.013	-1.89
2,6-$(CD_3)_2$-3,5-$(CH_3)_2$	7.96 [c]	3.24	0.014	-1.85
2,3,4,5,6-$(CH_3)_5$	8.75	3.5 [d]	0.015	-1.82
2,4,6-$(CD_3)_3$-3,5-$(CH_3)_2$	8.83 [c]	5.23 [e]	-	-
B. Quaternization with methyl iodide-d_3 (CD_3I)				
3,5-$(CH_3)_2$	6.15	597	2.61	0.42
2,3,5,6-$(CH_3)_2$	7.91	3.31	0.014	-1.84
2,6-$(CD_3)_2$-3,5-$(CH_3)_2$	7.96 [c]	3.59	0.016	-1.80
2,3,4,5,6-$(CH_3)_5$	8.75	4.0 [d]	0.017	-1.76
2,4,6-$(CD_3)_3$-3,5-$(CH_3)_2$	8.83 [c]	4.7 [d]	0.021	-1.69

[a] Refs 14,19

[b] C. Roussel unpublished

[c] Corrected data by constant increment, cf Ref. 14.

[d] Obtained by graphical extrapolation at 298 °K.

[e] Value at 302.9°K.

Table 2 : Logarithms of relative quaternization rate constants for polymethylpyridines[a,b]

Pyridine / Halide	3,5-$(CH_3)_2$	2,3,5,6-$(CH_3)_4$	Idem 2,6-D_6	Δ	2,3,4,5,6-$(CH_3)_5$	Idem 2,4,6-D_9	Δ
CD_3I	0.42	-1.84	-1.80	0.04	-1.76	-1.69	0.07
CH_3I	0.36	-1.89	-1.85	0.04	-1.72	-	-
Difference[a] Δ	0.06	0.05	0.05	-	0.06	-	-

[a] The difference Δ is the total isotope effect log k_D/k_H : between two horizontally adjacent values it indicates the rate increase on deuteriating the pyridinic α (γ)-methyl groups; between two vertically adjacent values it indicates the rate increase on deuteriating the methyl iodide.

[b] The values in the Table have an estimated error of at most 3%, with the exception of those for pentamethylpyridines where the error is at most 5 % because of the graphical interpolation.

3- Discussion of the results : CH_3/CD_3 - substituted pyridines

Since the deuterium atoms do not participate directly in the bond-forming or bond-breaking process, the kinetic isotope effect which is observed is classified as a secondary one, and as such it could be either positive (acceleration, as observed here) or negative (retardation).

The acceleration could be due to one or to both of the following causes : (i) the CD_3 group acts as a donor in comparison to CH_3 and as such it increases the basicity of deuteriomethyl pyridines ; (ii) the CD_3 group has smaller space requirements than the CH_3 group.

Brown and McDonald's k_D/k_H data at 25° C for the reaction between methyl iodide and deuteriomethylpyridines[8] are as follows : 4-Me, 1.001 ± 0.003 ; 3-Me, 1.009 ± 0.003 ; 2-Me, 1.030 ± 0.003 ; 2,6-Me_2, 1.095 ± 0.003. The higher rates with alpha mono and especially with ortho-ortho'-dimethylpyridines cannot be explained without the intervention of steric effects.[20]

An open question left by these experiments was whether steric effects account totally or partly for the observed acceleration. The 3-methylpyridine result favours the intervention of some electronic effect while surprisingly enough data for 4-methylpyridine do not confirm this tendency. By means of calorimetric measurements, Brown et al.[21] established that the heat of reaction of boron trifluoride with 2,6-lutidine increases significantly on replacing methyl hydrogens by deuterium atoms. In contrast, the

[8] H.C. Brown and G.J. McDonald, J. Amer. Chem. Soc., 88, 2514 (1966).

[20] H.C. Brown, "Boranes in Organic Chemistry", Cornell University Press, Ithaca N.Y. 1972.

[21] H.C. Brown, M.E. Azzaro, J.G. Koelling and G.J. McDonald, J. Amer. Chem. Soc., 88, 2520 (1966).

heats of reaction between BF_3 and other deuteriated methylpyridines, or the heats of reactions between the smaller diborane and any deuteriated methylpyridine, present differences which are too low in comparison with the experimental errors to allow a significant conclusion about the presence or absence of electronic factors being involved, in addition to steric factors, in these secondary isotope effects.

If CD_3 substituents are assumed to exert their secondary isotope effect in the quaternization of methyl-substituted pyridines both on the basis of steric and of inductive effects, then a clean separation between these two independent contributions can be performed as long as one knows the pK_a increment and the Brønsted coefficient at the given temperature for the given solvent.

$$\log k_{rel} = apK_a + C \qquad \text{(Figure 2)}$$

The coefficient is known for acetone (our data) : a = 0.36 for a wide range of pK_a variation [15c] for the alkylation of 3-and 4-substituted pyridines by methyl iodide in acetone. Recently Johnson et al.[22] reported a very similar value for the quaternization of the same compounds by EtI : 0.356. This result clearly shows that the same coefficient can be used in quaternization with CH_3I and CD_3I. Reactions in nitrobenzene (Brown'data) have a slightly different coefficient[22] which was used in the calculations given in Table 3 (last three entries).

To estimate the steric component of the observed secondary isotope effects, the pK_a values were calculated after Batts and

[15c] U. Berg, R. Gallo, G. Klatte and J. Metzger, J. Chem. Soc. Perkin II, 1350 (1980).

[22] C.D. Johnson, I. Roberts and P.G. Taylor, J. Chem. Soc. Perkin II, 409 (1981).

Spinner[13] and Balaban et al.[14], and the inductive component was substracted from the total isotope effect.

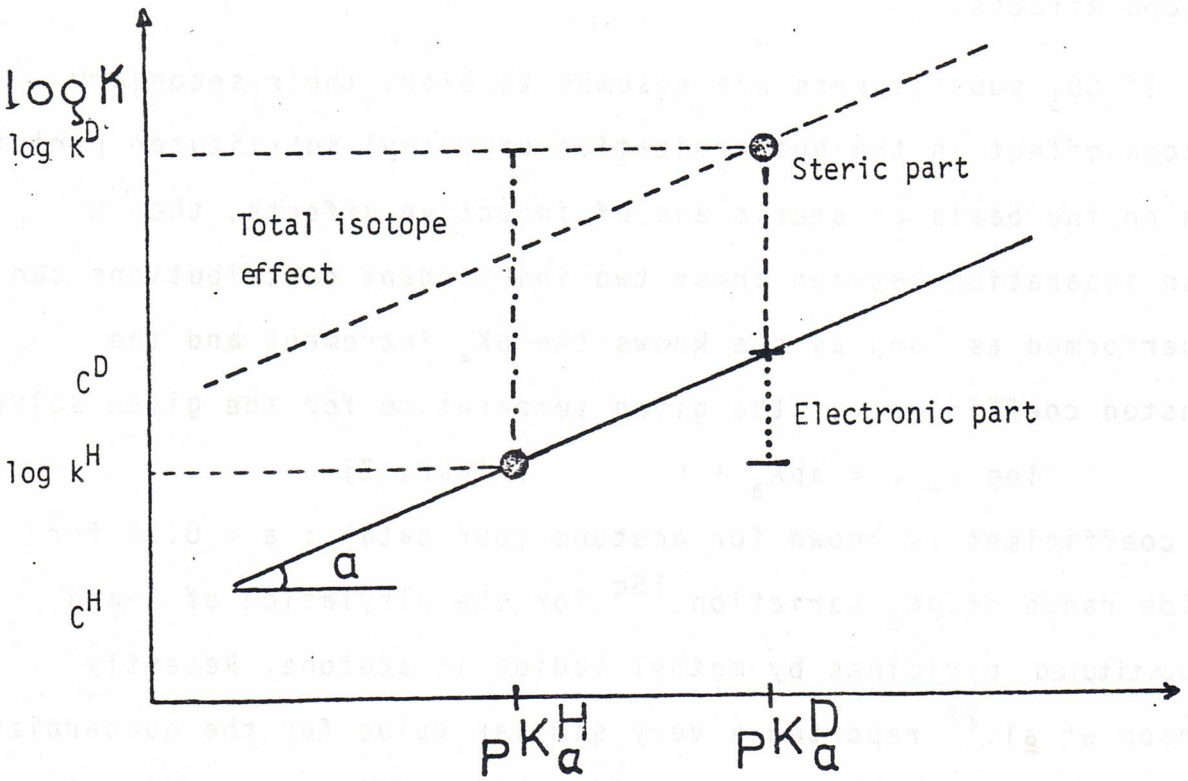


Figure 2 : Dissection of the total isotope effect (represented in a Brönsted diagram [23]) into a steric and an electronic component.

$\log k^H = apK_a{}^H + C^H$, $\log k^D = a\ pK_a{}^D + C^D$

$\log k^D/K^H = a\ (pK_a{}^D - pK_a{}^H) + (C^D - C^H)$

$(C^D - C^H)$ is the steric component, whereas $(a\ \Delta\ pK_a)$ is the electronic component of the total isotope effect.

[13] B. D. Batts and E. Spinner, J. Chem. Soc., 789 (1968).

[14] A.T. Balaban, I.I. Stanoiu and E. Gard, Rev. Roumaine Chim., 22, 1191 (1977).

[23] J.N. Brönsted, Z. Physik. Chem., 102, 169 (1922) ;
J. Shorter in "Advances in Linear Free Energy Relationships" (eds. N.B. Chapman and J. Shorter), Plenum Press, New York 1972.
L.W. Deady, W.L. Finlayson and O. L. Korytsky, Aust. J. Chem. , 32, 1735 (1979).

The data of Table 2 can thus be converted into relative units i.e. 100 (k_D/k_H - 1) %, and decomposed into an inductive and a steric component as seen in Table 3. It may be observed that the two components have approximately equal weights whenever the pyridine has two α-methyl substituents, but with one or no α-methyl substituent there is little or no detectable steric component of the secondary isotope effect. As expected the steric component increases on going to the more buttressed compounds.

Table 3 : Steric and inductive (electronic) components or the secondary isotope effects in the quaternization of CH_3/CD_3- or H/D-substituted pyridines.

Halide	Pyridine	Secondary isotope effects (%)			
		Total	Inductive	Steric	Ref.
CH_3I	2,3,5,6-Me_4	11.0	4.9	6.1	a
CD_3I	2,3,5,6-Me_4	8.5	4.9	3.6	a
CD_3I	2,3,4,5,6-Me_5	17,5	7,9	9,6	a
CH_3I	2,6-Me_2	9.5	4.9	4.6	8
CH_3I	2-Me	3.0	2.3	0.7	8
CH_3I	pyridine	3.1	-	-1.4	13
CH_3I	Pyridine-4d_1/d_o	1.2	-	-	13

[a]Present work, maximum error 3 % for the first two entries and 5 % for the last one.

4- Discussion of the results CH_3I/CD_3I

When the quaternization of the same substrate is performed with CD_3I instead of CH_3I, a small acceleration is observed as indicated in Tables 1 and 2, expressed in relative units. With all substrates for the quaternization, replacement of CH_3I by CD_3I causes an acceleration of 13 ± 2 % which is, surprisingly enough, independent of steric factors in the pyridine (i.e. of the presence or the absence of α-methyl groups).

Table 4 : Isotopic effects in the quaternization of the same substrate with CD_3I or CH_3I, expressed by 100 (k_D/k_H-1), %.

Substrate	Isotope effect
3,5-dimethylpyridine	14.6 ± 1.6
2,6-$(CD_3)_2$-3,5-$(CH_3)_2$-Py	11.0 ± 3
2,3,5,6-$(CH_3)_4$-Py	13.0 ± 3
2,3,4,5,6-$(CH_3)_5$-Py	14.0 ± 3

In the present case, the deuteriums are attached to the carbon atom which becomes bonded in the reaction, thus they could exert electronic and steric effects. Such secondary isotope effects in the quaternization of pyridine and 2-picoline were thoroughly discussed by Leffek et al.[24] without reaching a definite conclusion as to the relative importance of steric versus electronic origins of the acceleration observed on deuteriating

[24] K.T. Leffek and J.W. MacLean, Can. J. Chem., 43, 40 (1965) ; K.T. Leffek and A.F. Matheson, ibid., 50, 982, 986 (1972).

the alkyl iodide. During the approach of the reagents and in the transition state, the lower steric requirements of deuterium relative to protium ought to be reflected in an inverse accelerating isotope effect as observed. On the other hand, the inductive electron-releasing effect of C-D bonds could also stabilize the partial positive charge of the methyl in the TS and thus contribute to the observed acceleration. However, it is difficult to separate the isotopic effect into steric and electronic components.

5- Results for pentamethylpyridine, and their interpretation

Earlier experiments have indicated for pentamethylpyridine an appreciably higher value (11 times higher than the present data) which was not in line with the general behaviour of polymethylpyridines and seemed to point to an appreciable gear effect operating in this compound.[25] However, careful and repeated checking of these data did not reproduce the initial values and led to the extrapolated value given in Table I.

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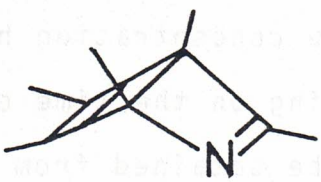
However, it was noted that unlike all the other pyridines which have been examined, the rate of quaternisation for pentamethylpyridine or its deuteriated congener does not present clean bimolecular kinetics, at the very begining of the reaction. This is clearly evidenced if one considers the relation between the conductivity (which is related to the concentration of pyridinium salt) and the time. The kinetics follow a clean bimolecular rate law after the first 0.2 % of the total pyridine concentration has entered the reaction, (Figure 3). Thus, depending on the time of the kinetic experiment, larger rate constants can be obtained from

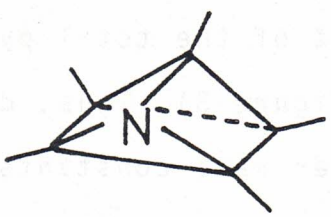
[25] Unpublished results presented in the Int[al] Symposium of Heterocyclic Chemistry, Bratislava July 1975. C. Roussel, H. Sanders, M. Chanon

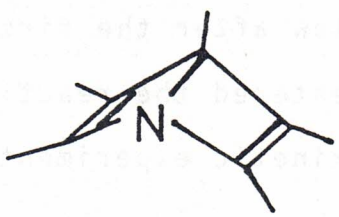
these data.

Independent experiments have indicated that traces of water cannot be responsible for the anomaly of pentamethylpyridine which is the only one of the polymethylpyridines to be very hygroscopic and to afford a crystalline hemihydrate. Therefore, the only plausible explanation for the non-linear behaviour (Figure 3) is the presence in small amounts (lower than 0.5 %) of a stronger nucleophile as an impurity. By the method of preparation (alkene diacylation) and purification, any such impurity would belong to the pyridine class with methyl substituents in ortho position. However, the most reactive of such pyridine, namely 2,4,6-trimethylpyridine reacts only ten times faster than the extrapolated value for pentamethylpyridine whereas the impurity has to be 10^3 times more reactive to account for the observed non-linearity.

Therefore, we believe that the only possible explanation for this anomaly is the presence of one of the valence isomers of pentamethylpyridine : pentamethylazaprismane and the two possible pentamethylsubstituted Dewar pyridines[26]. Pentamethyl azaprismane and the Dewar pyridine with nitrogen at the bridge head position should exhibit a very high nucleophilicity compared to the pentamethylpyridine analogue.







[26]A.T. Balaban, Rev. Roumaine Chim., 19, 1323 (1974).

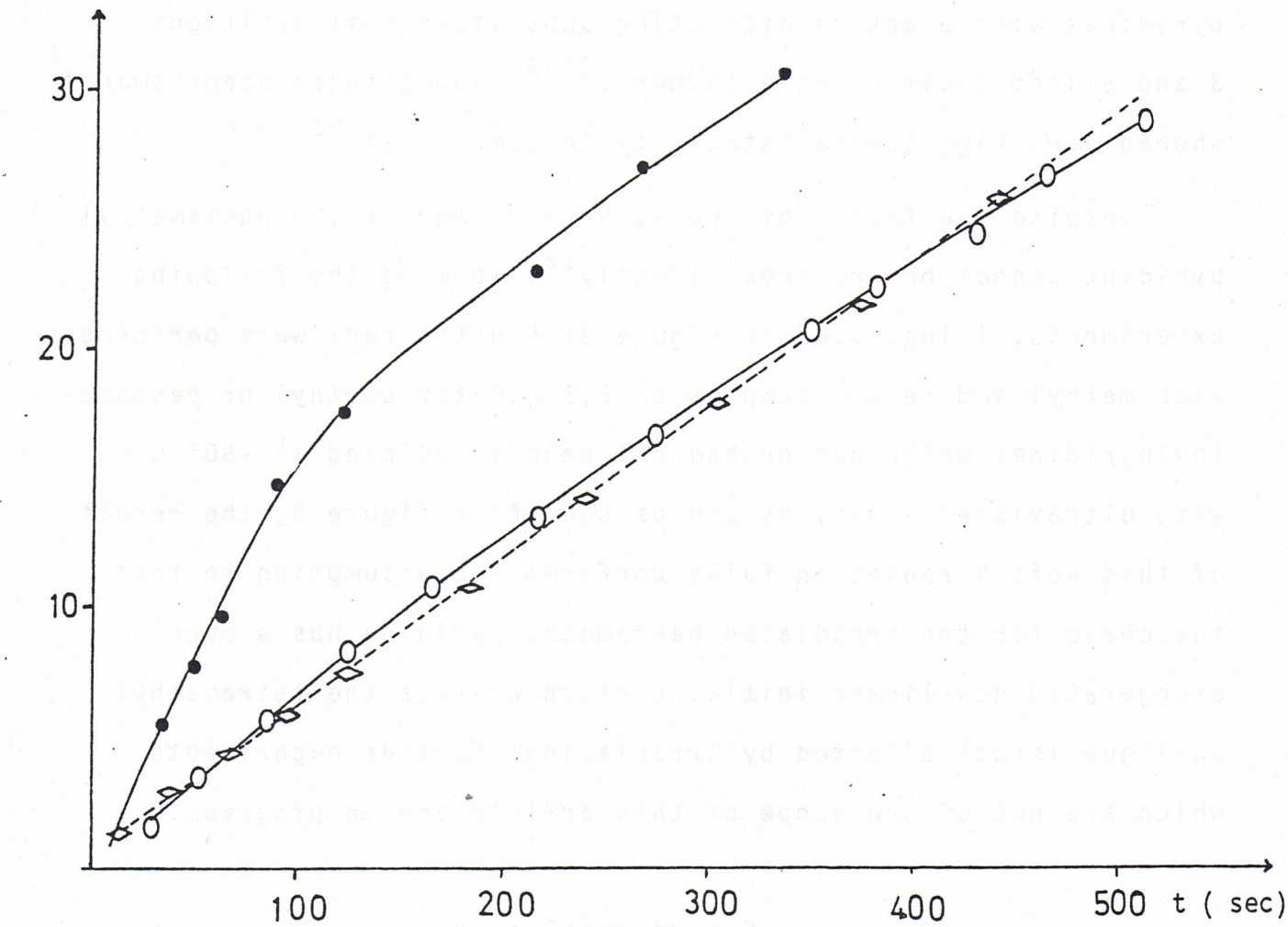


Figure 3 : quaternization of polymethylpyridines in acetone (25°C) by methyl iodide: anomalous behaviour of pentamethylpyridine.

O Pentamethylpyridine + MeI without irradiation of the pyridine sample

● Pentamethylpyridine + MeI after irradiation of the pyridine sample

◇ Normal kinetic curve for 2,3,5,6-tetramethylpyridine with or without irradiation of the pyridine sample.

Photochemical reactions are known to convert pentasubstituted pyridines with electron attracting substituents at positions 3 and 5 into their valence isomers.[27-30] Substituted azaprismanes showed very high thermal stability in some cases.[31]

Despite the fact that the valence isomer of the pentamethyl pyridine cannot be prepared directly[28], we made the following experiments, illustrated in Figure 3. Kinetic runs were performed with methyl iodide and samples of 2,3,5,6-tetramethyl or pentamethylpyridines which had or had not been irradiated at -80° C with ultraviolet light. As can be seen from figure 3, the result of this soft irradiation fully confirms the assumption in that the curve for the irradiated pentamethylpyridine has a much exaggerated non-linear initial portion whereas the tetramethyl analogue is not affected by irradiation. Further experiments which are out of the scope of this article are in progress.

Experimental part

A- Preparation of pyridines and Deuteriated Pyridines

Commercial pyridine and 3,5-dimethylpyridine were purified by preparative GLC with a stainless steel column (3.5 m x 1/4 in),

[27] M.G. Barlow, R.N. Haszeldine and J.G. Dingward, J. Chem. Soc. Perkin I, 1542 (1973).

[28] Y. Koloyashi, A. Ohsawa, M. Bala, T. Sato and I. Kuwadaki, Chem. Pharm. Bull. (Jpn), 24, 2219 (1976).

[29] R.D. Chambers, R. Middleton and R.P. Corbally, Chem. Commun. 731 (1975).

[30] T.J. van Bergen and R.M. Kellog, J. Amer. Chem. Soc., 94, 8451 (1972).

[31] R.D. Chambers and R. Middleton, J. Chem. Soc., Perkin I, 1500 (1977).

packed with Chromosorb P AW (60/80), 5 % KOH, and 20 % Apiezon L. Subsequently, they were distilled from potassium hydroxide.

2,4,6-Tri ($^2H_3$) methyl pyridine was obtained from 2,4,6-tri-(($^2H_3$) methyl) pyrylium perchlorate, prepared in turn by refluxing for two hours one part of 2,4,6-trimethylpyrylium perchlorate [32] in ten parts of D_2O, cooling, filtering, and repeating the process twice with fresh portions of 99 % D_2O. Finally, the ^1H-NMR spectrum (in TFA) shows that the perchlorate contains less than 1.5 % aliphatic protium atoms. The aromatic protons do not exchange under these conditions and serve as a standard for integral curves. The perchlorate was then treated in the cold with excess aqueous ammonia in the presence of diethyl ether. The ethereal layer was treated with 10 % HCl, the acid layer after ether extraction was treated with excess NaOH, and the product was extracted with ether, dried over NaOH, and distilled, b.p. 56° C/11 Torr. The NMR spectra showed that less than 2 % aliphatic protons were left. No impurity was evidenced by GLC.

2,3,5,6- Tetramethylpyridine was prepared according to the literature [33,34] and recrystallized from light petroleum, m.p. 76°C.

2,6-Di(($^2H_3$) methyl)-3,5-dimethylpyridine. The ether-insoluble layer containing the mixture of the two pyrylium perchlorates obtained in the diacylation of pentan-2-ol [33] was treated with concentrated aqueous KCl in order to convert de perchlorates into chlorides. The mixture was filtered and the filtrate was concentrated on a steam bath at reduced pressure (during the concentration

[32] A.T. Balaban and C.D. Nenitzescu, Org. Synth. Coll. Vol. 5, 1106 (1973).

[33] P.F. G. Praill and A.L. Whitear, J. Chem. Soc. , 3573 (1961).

[34] H.G. Rajoharison, C. Roussel and J. Metzger, J. Chem. Res. S-186, M-2157 (1981).

extra filtrations are necessary). The residue containing the pyrylium chlorides was refluxed with a 50-molar excess of D_2O as in the case of 2,4,6-trimethylpyrylium, but each time evaporating under vacuum the H_2O/D_2O mixture on the steam bath. Treatment with ammonia afforded the pyridines and the desired compound was obtained by crystallization form light petroleum. The deuteriation amounted to 98 % (NMR). NMR δ ($CDCl_3$) 2.18 (3,5-Me_2), 7.03 (4-H).

Pentamethylpyridine was obtained from pentamethylpyrylium perchlorate. On diacetylating 3-methylpentan-3-ol with Ac_2O and 70 % $HClO_4$, and treating the dark reaction mixture with ether as in the preceding case, an ether-insoluble layer was obtained which contained pentamethylpyrylium and 4-ethyl-2,3,6-trimethylpyrylium perchlorates. The two corresponding pyridines were obtained in admixture after treatment with aqueous ammonia.[35,36] In order to obtain pure pentamethylpyridine, the mixture was left overnight in a wide dish : only the pentamethylpyridine was left as the less volatile crystalline hemihydrate, and it was purified by recrystallization from light petroleum, yielding leaflets, m.p. 48° C. On distillation under reduced pressure, pure liquid pentamethylpyridine was obtained (b.p. 90° C/10 Torr), but brief exposure to the atmosphere converted it into the hemihydrate and thus exceptional precautions were used to prevent any hydration.

[35]A.T. Balaban, A. Bota, F. Chiraleu, E. Sliam, A. Hanes and C. Draghici, Rev. Roumaine Chim., 22, 1003 (1977).

[36]H.G. Rajoharison, H. Soltani, M. Arnaud, C. Roussel and J. Metzger, Synthetic Commun., 10, 195 (1980).

M. Arnaud, A. Pedra, C. Roussel dans J. Metzger, J. Org. Chem., 44, 2979 (1979).

2,4,6-Tri(($^2H_3$)methyl)-3,5-dimethylpyridine was obtained from the corresponding pyrylium salt. The perchlorates in the ether-insoluble layer from the preceding experiment were converted into chlorides by treatment with aqueous KCl. The resulting $KClO_4$ was filtered off and the aqueous layer concentrated under vacuum. This was followed by addition of a 100-fold molar excess of D_2O relative to pyrylium, refluxing for three hours, evaporation under reduce pressure, and by two further deuteriation cycles. The conversion of the crude mixture of pyrylium perchlorates into chlorides in this and the preceding case was necessary (i) to avoid diluting the deuterium oxide with water and (ii) to be able to concentrate the solution without danger of explosion.

The mixture of deuteriated pyrylium salts was treated with excess NH_4OH and the deuteriated pentamethylpyridine was freed from its isomer by conversion into the crystalline hemihydrate, which was purified by recrystallization from light petroleum, drying over CaH_2 or $LiAlH_4$ in anhydrous ether, and vacuum distillation under protection from moisture. The deuteriation amounted to 98 % (by ^1H NMR). NMR δ ($CDCl_3$) 2.16 ppm (singlet).

B- Preparation and Purification of Reagents and Solvents

Acetone, dried and fractionated over K_2CO_3 was stored over 4 A molecular sieves. Methyl iodide and CD_3I (Fluka reagents) were distilled from, and conserved over, mercury in the absence of light. All flasks were wrapped in aluminium foil and kept for a maximum of two days in the refrigerator. Solutions were transferred by means of weighed syringes. Solutions of pyridines in acetone were prepared in 25 ml volumetric flasks.

C- Conductimetric Determination of the Rates of Quaternization

The conductimetric method has been described periously [16,18]

For calibration of the cell, pure triiodide-free polymethylpyridinium iodides were prepared by leaving in the dark for 24h . . 1.0. molar acetone solutions of the pyridines with excess methyl iodide. The supernatant liquid was then decanted, and the crystals were purified in the absence of moisture, oxygen and light and under nitrogen so as to avoid trace of triiodides.

Hexamethylpyridinium iodide, m.p. 183° C after nine recrystallizations, hygroscopic crystals. Found : C, 44.9 ; H, 6.1 ; N, 4.6. Calcd. for $C_{11}H_{18}IN$, C, 45.4 ; H, 6.2 ; N, 4.8 %. ^1H NMR δ ($CDCl_3$) 2.45 (3,4,5-Me_3), 2.78 (2,6-Me_2), 4.36 (1-Me). UV (CH_3CN) 275 nm, but in $CHCl_3$ a charge-transfer band appears with maximum at 324 nm.

1,2,3,5,6-pentamethylpyridinium iodide, m.p. 178-9° C after eight recrystallizations, colourless crystals. Found : C, 43.3 ; H, 5.8 ; N, 5.1. $C_{10}H_{16}IN$ requires : C, 43.3 ; H, 5.8 ; N, 5.1 %. ^1H Nmr δ ($CDCl_3$) : 2.50 (3,5-Me_2), 2.85 (2,6-Me_2), 4.36 (1-Me), 7.94 (4-H). UV in CH_3CN 285 nm, but in $CHCl_3$ a CT band at 344 nm appears.

1,3,5-Trimethylpyridinium iodide, m.p. 269° C after five recrystallizations. Found : C, 38.4 ; H, 4.8 ; 5.6. Calcd. for $C_8H_{12}IN$, C, 38.6 ; H, 4.9 ; N, 5.6 %. ^1H NMR δ ($CDCl_3$) : 2.48 (3,5-Me_2), 4.33 (1-Me), 8.30 (4-H), 8.86 (2,6-H_2). UV in CH_3CN 285 nm, CT band in $CHCl_3$ at 365 nm in agreement with the literature.[37]

The calibration factors of these three salts were respectively at 10°C and 30° C : 0.754, 0759, 0,748 and 0889, 0892, 0,882 1/mol ohm.

The rate constant determinations were performed at different temperatures and calculated at 25° C by means of the Eyring equation.

[37] E.M. Kosower and J.A. Skorcz, J. Amer. Chem. Soc., 82, 2195 (1960).

Examples : Rate constants determinations

3,5-dimethylpyridine :

		T(K°)	k_T $(10^{-6})^a$	k_{298} $(10^{-6})^b$
CH_3		292.95	357 ± 10.0	520.
	I	298.30	530.4 ± 4.4	518.9
	II	298.30	538.8 ± 3.4	527.1
		302.95	742.3 ± 10.2	519.7
				521.4 ± 3.8
CD_3I		298.40	697.3 ± 3.8	589.1
	I	292.95	404.3 ± 2.5	598.4
	II	292.95	405.5 ± 2.8	600.2
	III	302.95	855.9 ± 5.1	590.1
	IV	302.95	883.5 ± 9.9	609.1
				597 ± 8.2

[a] Crude rate constant at the given temperature and standard deviation from least square analysis on 14-20 experimental points.

[b] Obtained from Eyring equation.

2,3,5,6-Me_4-pyridine with CD_3I

T(°C)		$K_T(10^{-6})$	$K_{298}(10^{-6})$
20.95	I	4.88	3.249
		4.97	3.309
		4.86	3.236
	II	5.106	3.399
		5.118	3.407
25.3	II	3.41	3.325
19.95	I	2.09	3.208
	II	2.13	3.270
		2.18	3.347
			3.305 ± 0.07

2,6-(CD_3)-3,5-Me_2 with CD_3I

29.95	5.532	3.64
	5.281	3.48
	5.476	3.61
25.3	3.83	3.73
19.95	2.26	3.51
		3.59 ± 0.10

Examples : checking of second order kinetic runs

3.5 diméthylpyridine

	Pyridine Mol/2	Alkylation agent Mol/l	$k_{298}(10^{-6})$
CH_3 I	0.00774	0.00448	518.9
	0.00448	0.00774	527.1
CD_3 I	0.00496	0.00819	598.
	0.00744	0.00545	600.
	0.00496	0.00819	590.0
	0.00744	0.00546	609.