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NUCLEOPHILIC CHARACTER OF ALKYL RADICALS—VII[1]

SUBSTITUENT EFFECTS ON THE HOMOLYTIC ALKYLATION OF PROTONATED HETEROAROMATIC BASES WITH METHYL, PRIMARY, SECONDARY AND TERTIARY ALKYL RADICALS

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Abstract—The relative rates of the homolytic alkylation of protonated 4-substituted pyridines with methyl, n-propyl, n-butyl, sec-butyl and t-butyl radicals, obtained by the silver-catalyzed decarboxylation of acids with ammonium peroxydisulphate, are reported. This is the first time that the reactivities of the main alkyl radicals have been compared using the same reagent model in a homolytic aromatic alkylation. The alkylation takes place exclusively in the 2 position and the chemical reactivity parameters correlate well with the chemical shifts, but not with the Hammett σ_m constants because of an enhanced conjugation of the electron-releasing substituents. The influence of the polar characteristics on the t-butyl radical is very striking. The results are discussed in terms of a π-complex transition state.

AROMATIC HOMOLYTIC ALKYLATION has received little attention with respect to arylation, in regards both the synthetic and theoretical aspects, and thus several factors which influence the mechanism are not clear. Extensive studies have been made only with methyl[2] and cyclohexyl[3] radicals; it is difficult, therefore, to have a satisfactory evaluation of the influence that the structure of the alkyl radical has on the reactivity, particularly with respect to the effect that the polar characters of both the radicals and substrates have on the reaction rates. This is mainly due to the fact that reactions in the homocyclic series are generally not clean, but appreciable amounts of secondary products are formed. Very reliable information concerning the relative rates of attack on such compounds cannot be gained by the analysis of the alkylation products of either simple or competitive reactions of this kind, owing to the complex nature of the complete reactions between homocyclic aromatic substrates and alkyl radicals. Thus the techniques which have been used successfully for the homolytic arylation are of little use in this case.[4]

We have recently claimed[1,5,6] that the homolytic alkylation of protonated heteroaromatic bases has very high synthetic interest, comparable to electrophilic alkylation in the homocyclic series, because of the availability of many inexpensive alkyl radical sources, simple experimental conditions, high yields, selectivity and versatility. Moreover, the normal absence of secondary products from heteroaromatic substrates

led us to consider these reactions as particularly interesting models for the study of alkyl radical reactivity.

The synthetic and theoretical interest in these reactions was ascribed to the nucleophilic character of the alkyl radicals;[1,5] a quantitative study therefore was useful for understanding the mechanism of the reaction and for evaluating the polar character of the alkyl radicals having different structures, which is still an open question. The problem has already been partially investigated by us[6] by studying the reactivity of protonated quinoxaline and quinoline with alkyl radicals, which revealed that quinoxaline was more reactive than quinoline and that the difference in reactivity increased from primary to secondary and tertiary radicals. One of the simplest criterion for deciding whether a given radical is electrophilic or nucleophilic is examination of a particular series of substrates in terms of the Hammett $\sigma-\rho$ relation. This criterion was used in this investigation to study the reactivity of the methyl, primary, secondary and tertiary alkyl radicals, as well as to investigate the mechanism of the homolytic alkylation of heteroaromatic bases.

RESULTS AND DISCUSSION

To study quantitatively the effect of polar character on alkyl radical reactivity, relative reaction rates were determined with 4-substituted pyridines in an acidic medium. This model is particularly suitable for the following reasons: (i) the reaction is very clean and secondary products are not formed; (ii) the reaction is completely selective and only the α position is attacked in all cases; (iii) as the substituent is in the *meta* position with respect to the position of attack of the alkyl radical, the resonance stabilization effects of the substituent are minimized and this permits isolation of the polar effects.

The alkyl radicals were obtained by the silver catalyzed oxidative decarboxylation of acids by ammonium peroxydisulphate,[7] which was found to be particularly useful in the homolytic alkylation of protonated heteroaromatic bases.[1] The great versatility of this radical source permits methyl, primary, secondary and tertiary alkyl radicals to be obtained under the same experimental conditions.

The competitive method was used, working with an excess of heteroaromatic bases in aqueous sulphuric acid solution, so that the products ratio directly gave the relative reaction rates. The results obtained with methyl, n-propyl, n-butyl, sec-butyl and t-butyl radicals are summarized in Table 1.

With the t-butyl radical, in addition to cyano, acetyl, hydrogen, methyl and

TABLE 1. RELATIVE REACTIVITIES FOR THE HOMOLYTIC ALKYLATION OF PROTONATED 4-X-PYRIDINES

R· / –X	Me	n-Pr	n-Bu	sec-Bu	t-Bu
CN	12·45	19·70	20·30	259·00	1890
$COCH_3$	3·60	5·57	5·60	55·60	144
Cl	2·38	—	—	—	11·12
H	1·00	1·00	1·00	1·00	1·00
CH_3	0·53	0·35	0·32	0·28	0·15
OCH_3	0·27	0·12	0·10	0·02	0·0054

methoxy groups, it was necessary to insert chlorine in the series, as the difference in reactivity between 4-acetyl-pyridine and pyridine was too great to allow the direct determination with sufficient analytical accuracy; the chloro-derivative was also used with the methyl radical to obtain a comparison with the t-butyl radical.

These results clearly show that on the basis of the orientation and reactivity, all the alkyl radicals examined have net nucleophilic character and this character gradually increases from the methyl to primary, secondary and tertiary alkyl radicals. A very striking feature is the selectivity shown by the t-butyl radical: in fact there is a factor of $3{\cdot}5 \times 10^5$ difference between the reactivities of 4-cyano- and 4-methoxy-pyridine, which is much greater than that found for the methoxydechlorination of 4-cyano-2-chloro- and 4-methoxy-2-chloro-quinolines[8] (3×10^3).

This is the first time that the reactivities of the main alkyl radicals have been directly compared in an homolytic aromatic substitution, using the same reagent model and the same experimental conditions, allowing the influence of the radical structure on its reactivity to be well defined. It is also the first time that polar effects of such great extent are revealed in a homolytic alkylation.

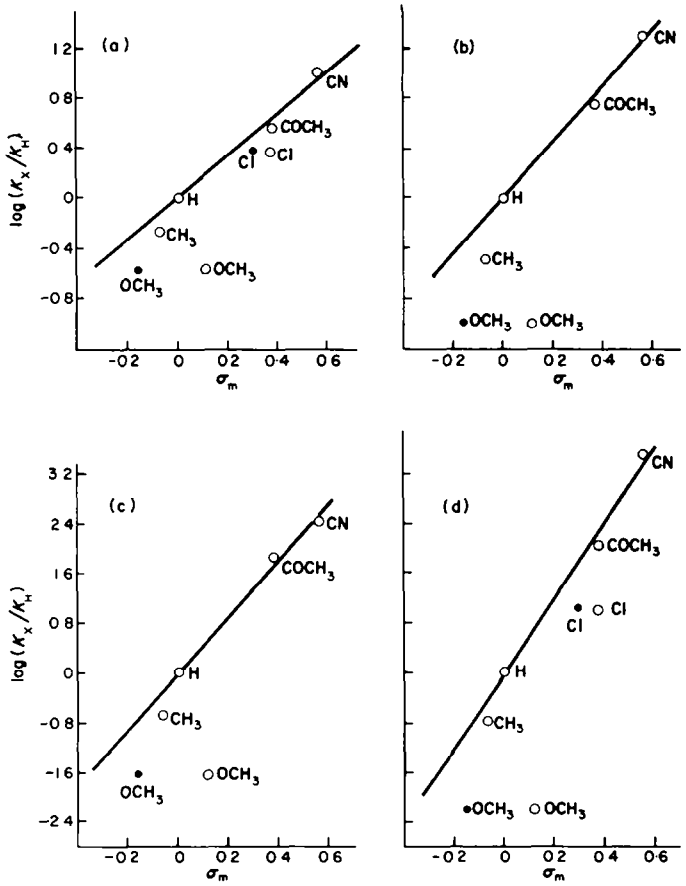


FIG. 1. Correlation of relative rates by σ_m constants in the alkylation of 4-X-pyridines, by methyl (1*a*), n-butyl (1*b*), sec-butyl (1*c*) and t-butyl (1*d*) radicals. ○ indicates Hammett's σ_m; ● indicates σ_m taken from ref. 8.

Plots of log (K_X/K_H) vs. σ_m (Fig. 1*a–d*) show that a Hammett correlation is not observed, mainly due to the fact that the methoxy group is deactivating, despite the positive value of its σ_m constant, and chlorine is less activating than would be expected from its σ_m constant. This behaviour is however substantially the same for all five of the alkyl radicals examined. Such behaviour has already been observed in classical nucleophilic substitution reactions, such as the methoxydechlorination of 4-substituted-2-chloro-pyridines[9] and quinolines,[8] in the homolytic methylation of 4-substituted pyridines[10] (in which the t-butyl hydroperoxide was employed as a source of methyl radicals), and in homolytic substitution at the *a* position of 4-substituted quinolines with the dioxanyl C-radical.[11] Therefore this is a very general phenomenon, that is peculiar of the pyridine ring towards nucleophilic species (ionic and radical) and that further confirms the nucleophilic character of the five alkyl radicals examined.

We also think that the interpretation of this behaviour must be the same for both the ionic and radical substitutions previously described. In fact the results can be well explained in all cases by an enhanced conjugation between the electron-releasing groups and the heterocyclic nitrogen.[8] This enhanced electron-releasing effect results in higher availability in the heteroaromatic ring, thus reducing the electron-accepting capacity in the rate determining step. The phenomenon would be accentuated in the case of the protonated bases:

In fact, also using the σ_m values calculated for the chlorine (+0·298) and the methoxy group (−0·157) that gave a linear correlation in the methoxydechlorination of 4-substituted-2-chloro-quinolines[8] (which obviously are not protonated), it can be seen that these values are inadequate as the methoxy group is more deactivating and chlorine less activating with respect to these σ_m values (Fig. 1*a–d*).

On the other hand, an enhanced electron-releasing effect cannot be promoted in the transition state, because of the nucleophilic character of the reagent; it is more probable that this fact be connected with the ground state of the protonated pyridines.

TABLE 2. CHEMICAL SHIFTS OF α-PROTONS AND pK_a OF PROTONATED 4-X-PYRIDINES

−X	Chem. shifts ppm (δ)	pK_a*
CN	9·3†	1·86
$COCH_3$	9·11	3·51
Cl	9·0†	3·83
H	8·86	5·23
CH_3	8·7†	6·02
OCH_3	8·56	6·62

* From ref. 24
† From ref. 23

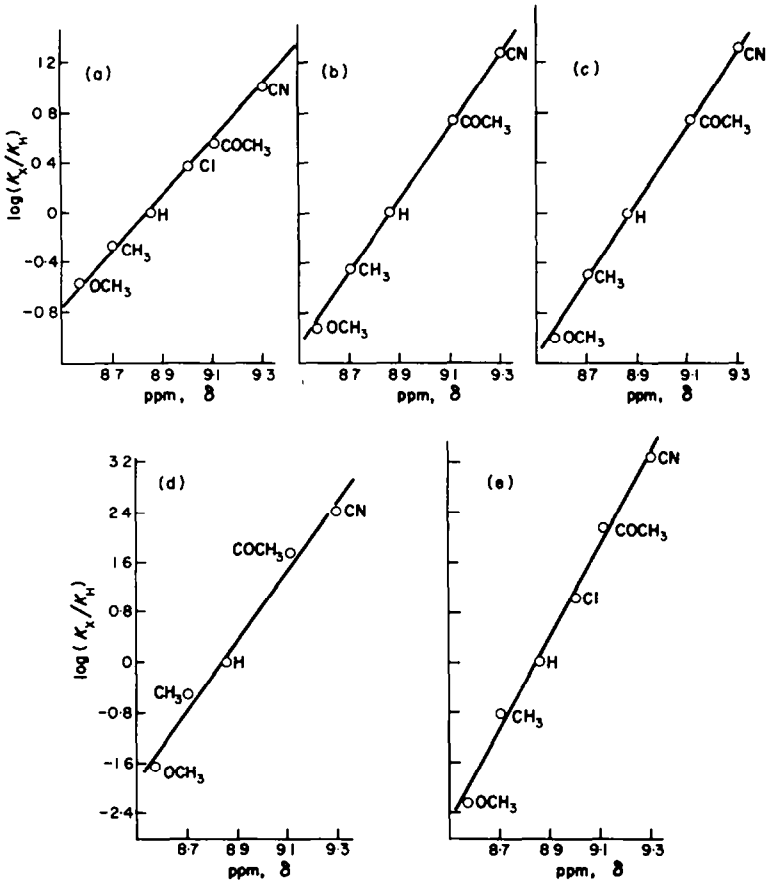


FIG. 2. Correlation of relative rates by chemical shifts of α protons in protonated 4-X-pyridines, by methyl (2*a*), n-propyl (2*b*), n-butyl (2*c*), sec-butyl (2*d*) and t-butyl (2*e*) radicals.

This induced us to correlate the relative rates with the chemical shifts of the protons in position 2 of the protonated pyridines (Table 2). Plots of log (K_X/K_H) vs. the chemical shifts are shown in Fig. 2*a–e*: in all cases a good correlation was observed. The slopes of the plots (Table 3) give a measure of the different selectivity of the five radicals examined; n-propyl and n-butyl have practically the same selectivity, as was expected.

It is interesting to point out that the chemical shifts of nuclei at the *meta*-position

TABLE 3. SLOPES FROM FIG. 2*a–e*

Alkyl radical R·	Slope
Me	2·224
n-Pr	3·014
n-Bu	3·130
sec-Bu	5·573
t-Bu	7·455

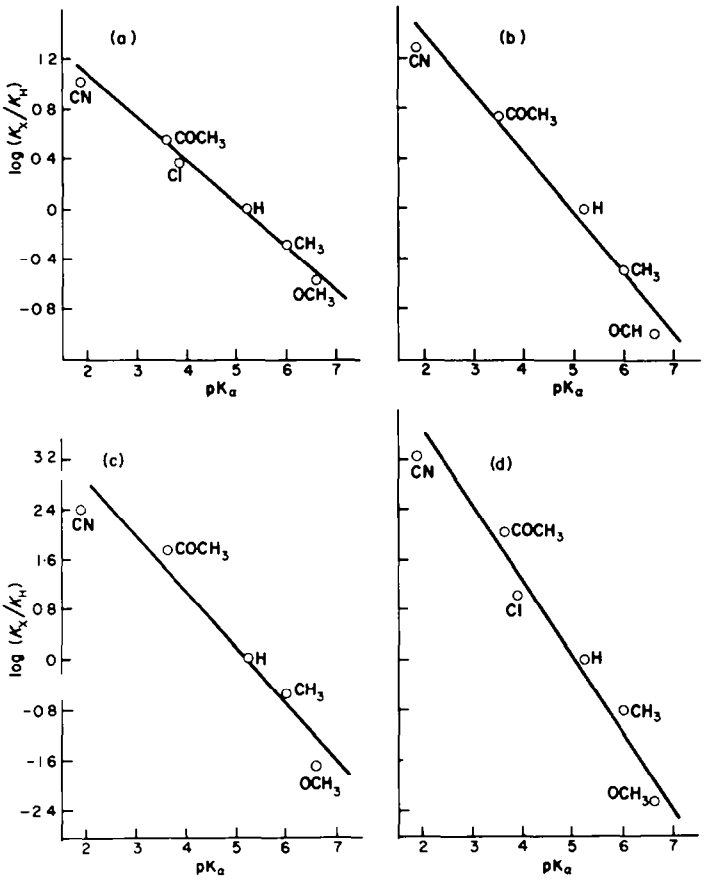


FIG. 3. Correlation of relative rates by pK_a of 4-X-pyridines in the alkylation by methyl (3*a*), n-butyl (3*b*), sec-butyl (3*c*) and t-butyl (3*d*) radicals.

show a very poor correlation with Hammett and Taft σ-constants.[12] It is the first time that such a good correlation has been observed between the chemical shifts in the *meta*-position and the chemical reactivity parameters. A rough correlation is also observed with the pK_a of the 4-substituted pyridines (Fig. 3*a–d*).

It would be extremely interesting to make a comparison of these data with the results of similar work on these radicals for both the homocyclic and heterocyclic series. In the heterocyclic series we have recently reported[10] the relative rates for the methyl radical obtained from t-butyl-hydroperoxide with the same reagent model here described; the behaviour was essentially identical apart from the somewhat higher selectivity, which was largely due to the lower reaction temperature (0°C) in comparison to that used in this work (90°). Of the five radicals used here, only methyl has been repeatedly used for quantitative studies in homocyclic series, but the reported data are few and insufficient.

This is probably due to the complexity of the reactions studied, which gave rise to side reactions that detracted from the theoretical significance of the experimental results on the relative alkylation rates of various aromatic compounds, and on the

ratios of isomeric alkylation products formed. In our opinion, both the incursion of side reactions and the poor yields which are usually the result of homolytic alkylation in the homocyclic series, in comparison to homolytic arylation, are mainly due to the nucleophilic character of the alkyl radicals. Thus, while the isomer distribution in the homolytic methylation has been repeatedly reported, the relative rates have not; some isolated data were not very conclusive; thus the rate of homolytic methylation of chlorobenzene relative to benzene was found to be 0·9 using the competitive method[2] and 4·2 using the indirect method of Szwarc.[13] More extensive data of partial rate factors have been reported for the homolytic cyclohexylation in the homocyclic series:[3] apart from the theoretical significance of the results, due to the large amounts of uninvestigated secondary products formed in the reaction, the extent of the polar effects is however rather modest in comparison to that found in our work. For example, substrates having different polar character such as anisole, chlorobenzene, fluorobenzene and trifluorotoluene had a reactivity of the same order of magnitude (2–3 times more reactive than benzene) and the difference of reactivity between benzonitrile and anisole was about 12, compared to the difference showed by the sec-butyl radical with respect to 4-cyano and 4-methoxy-pyridine (13×10^3, Table 1). Also considering the lack of sufficient data in the homolytic alkylation of homocyclic aromatics, it is clear that the extent of the polar effects of the substituents is much lower than that in the series of protonated pyridines. This substantial difference of selectivity in the homolytic alkylation of the homocyclic series and protonated heteroaromatic bases make the reaction particularly interesting in this latter case

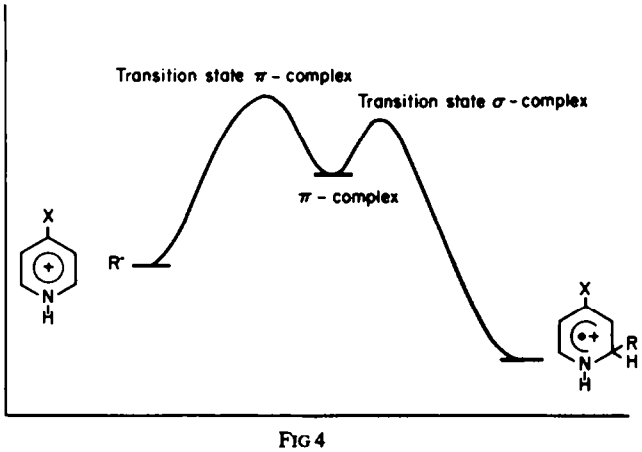
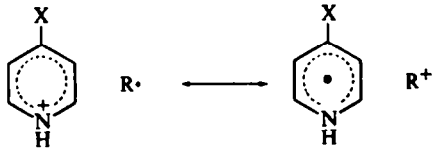


FIG 4

and can be, in our opinion, interpreted in terms of transition states. The difference in reactivity between protonated pyridines and benzene derivatives is so great that its experimental determination with the competitive method is not possible.[5] With strongly electron-deficient substrates, between the two limiting structures which one may assume for the transition state of the reaction, a σ-complex and a π-complex, it is the latter (Fig. 4) that best explains the observed results. Above all the good correlation between the chemical reactivity parameters and the chemical shifts would indicate that, in the transition state, a defined primary valence bond between the radical and the substrate is not developed, as in a σ-complex. No rehybridization

can be assumed but instead a mutual perturbation of the dispersion fields of the reactants, as in a π-complex, in which enhanced contribution of polar forms would explain the very high sensitivity to polar influence:



The correlation with the chemical shifts leads to the assumption that the anisotropic contribution and the intermolecular interactions are substantially identical or are secondary components. and that the major factor controlling both the chemical reactivity and the relative shielding of the hydrogen nuclei in the *meta* position to the substituent is the electron density in position 2 of the unperturbed ground state molecule.

Also the enhanced conjugation of the electron-releasing groups, which is connected with the ground state of the substrate, as are the chemical shifts, agree much more with a π-complex transition state than with a σ-complex. Instead, the reported results of homolytic alkylation in the homocyclic and not protonated heteroaromatic series,[14] even though insufficient, suggest that with non strongly electron-deficient substrates the transition state may be more similar to a σ-complex, in which a defined primary valence bond is developed between the radical and the substrate, which undergoes rehybridization. In this case the activation energy can be correlated with the atom localization energies, as was observed in the homolytic methylation of unsubstituted alternant aromatic hydrocarbons.[15] Factors other than polar can become prevalent in a transition state similar to a σ-complex and it is therefore not surprising that anisole, chlorobenzene and benzonitrile may all be more reactive than benzene in homolytic cyclohexylation, even though it is clear that the cyclohexyl radical is nucleophilic also in the homocyclic series,[3] and it was claimed that there is evidence that in general the isomer distribution obtained in homolytic methylation is similar to that obtained in phenylation.[16]

We recently showed[1,6] that the behaviour of the methyl and phenyl radicals was very different in the homolytic substitution of protonated heteroaromatic bases. This would be due to the fact that even in this latter case, because of the very poor polar character of the phenyl radical, the transition state would always be similar to a σ-complex, for which, for example, there is no great variation in reactivity and isomer distribution going from an unprotonated to a protonated heteroaromatic base.[17] Instead with an alkyl radical, passing from an unprotonated[14] to a protonated heteroatomatic base,[5] it would pass from a transition state similar to a σ-complex to one similar to a π-complex, for which the reactivity and the isomer distribution vary dramatically (both of these aspects contribute to the very high synthetic interest of the reaction in an acidic medium).

It was also reported[18] that the methyl radical is very slightly electrophilic in the hydrogen abstraction from *p*-substituted toluenes ($\rho = -0{\cdot}1$) and that hydrogen atom. methyl and phenyl radicals all have the same selectivity and are approximately electrically neutral.[19] We merely think that the hydrogen abstraction from benzylic

C—H bonds, being very exothermic, shows very poor sensitivity to polar effects due to a small amount of bond reorganization at the transition state.

Another aspect which merits brief comment is the possibility that the alkyl radicals may have dipolar character and therefore would react as nucleophilic or electrophilic species depending on the electron-deficient or electron-rich nature of the substrates. Such indication could arise from a recent study on the homolytic methylation of naphthalene, in which it was proposed that there is a contribution of polar forms with the electrophilic methyl radical.[20] Actually such an assumption is not justified: the solvent effects noted in this work can be equally well interpreted on the basis of the nucleophilic character of the methyl radical. On the other hand, electron-rich substrates, such as 1,3-dimethoxybenzene, do not show a particularly high reactivity in comparison to other benzene derivatives and above all they are much less reactive than the protonated heteroaromatic bases.

In conclusion, the intrinsic polar character of the methyl radical, and to a larger extent of the primary, secondary and tertiary alkyl radicals, can be considered as nucleophilic. This character is shown in macroscopic form only in those reactions in which the transition state allows a high contribution of polar forms.

From this point of view the model selected seems to us particularly suitable, and quantitative studies are in progress with more sophisticated nucleophilic carbon radicals (O-alkyl, N-alkyl, acyl and carbamoyl).

EXPERIMENTAL

All the pyridines used as substrates were distilled before the use: pyridine, isonicotinonitrile and methyl-(4-pyridyl)-ketone were commercial products; 4-chloro-pyridine was isolated from its commercial hydrochloride immediately before use; 4-methoxy-pyridine was obtained from the reduction of corresponding N-oxide with H_2 and Raney-Ni, according the procedure described for quinoline N-oxides.[21]

Most of the 2-alkyl-derivatives of the 4-substituted pyridines were known compounds.[1,22] Preparative GLC was used to obtain samples of all the alkyl pyridines produced in the competitive reactions (Varian Aerograph Model 90 P; 2000 × 4·5 mm steel column, packed with 10% SE 30 on Chromsorb W), which were tested for identification by NMR and mass spectroscopic techniques. A ratio 1:2 of the areas concerning to the absorption peaks due to the α and β aromatic protons respectively, was observed in all cases.*

The GLC analyses of the competitive reactions were performed on a Varian Aerograph, Series 1200, equipped with a flame ionization detector, using 2000 × 2·5 mm steel columns A or B according to the nature of the mixture. Column A: 5% SE 30 on Chromsorb W; column B: the packing material was prepared by supporting 1 g of Apiezon L and 1 g of Carbowax 20 M on 10 g of Chromsorb A/W (60–80) previously coated with 0·4 g of KOH.

In Table 4 the operative conditions employed in the GLC analyses of the reactions performed in this study are reported.

A correction was made in the calculation of the peak areas ratio, according to the experimental detector responses, determined on the corresponding pure sample previously isolated.

Apparatus and general procedure. A three-necked, round bottomed flask was fitted with a mechanical stirrer, a reflux condenser and an additional funnel with a pressure equalizer side arm. The soln of $(NH_4)_2S_2O_8$ (5 mmole) in little water was added in 30 min to a well stirred mixture of the two pyridines (Table 4), 3 M H_2SO_4 (10 ml) and the appropriate carboxylic acid (twofold the total molar amount of the pyridines); 0·05 g of $AgNO_3$ was also present. The apparatus was kept on a water bath (internal temp 90°) from the beginning till 30 min after the end of the addition of persulphate (total 60 min). After cooling the mixture was diluted with H_2O (50 ml), carefully basified with 3N NaOH to pH 10–12 under stirring and cooling, and extracted with ether. The combined ether extracts were concentrated to 10 ml by distillation,

* NMR data will be published elsewhere.

TABLE 4. COMPETITIVE REACTIONS EFFECTED: MOLAR RATIOS AND COLUMNS FOR GLC ANALYSIS*

Molar ratio (mmole)	R· / Substrates	Me		n-Pr		n-Bu		sec-Bu		t-Bu	
		Col.	T	Col.	T	Col.	T	Col.	T	Col.	T
10: 10	$CN/COCH_3$	A	90	B	140	B	170	B	130	A	150
10: 50	$COCH_3/H$	B	130	B	160	B	140	B	145	†	—
10:100	$COCH_3/CH_3$	B	160	B	190	B	160	B	180	†	—
10: 10	$COCH_3/Cl$	B	90	—	—	—	—	—	—	B	140
15: 50	Cl/H	B	90	—	—	—	—	—	—	A	120
10: 10	CH_3/OCH_3	B	90	B	120	B	130	B	120	B	120
10: 30	H/CH_3	B	75	B	80	B	100	B	100	B	80

* Isothermal temp.; carrier: N_2 at 30 ml/min.

† Not effected because of the great difference in reactivities.

and analyzed by GLC (Table 4). Also the ether distilled was tested by GLC to be sure that no alkylated pyridines were loss during the concentration. The results summarized in Table 1 are the average of two or three independent reactions.

Determination of the chemical shifts of the α-protons in 4-X-pyridines and pyridine. The chemical shifts of the protons in α-position for protonated isonicotinonitrile, 4-chloro- and 4-methyl-pyridine has been recently reported.[23] The chemical shifts of methyl-(4-pyridyl)-ketone and 4-methoxy-pyridine were recorded under the same conditions (0·5 M soln in TFA) with a Varian XL-100-15 spectrometer. Chemical shifts were measured from TMS as internal standard, using a frequency counter, which provides an accuracy in locating peak positions within ±0·02 Hz. The chemical shifts were calculated by partial analysis of the AA'BB'X type spectra, where X is the H-N^+ proton: δ_{AB} is sufficiently large to allow the easy identification of ν_1 and ν_3 frequencies, and thus the measure of $N = |J_{AB} + J_{AB'}|$ value from high field portion of the spectrum ($H_3 + H_5$). Once obtained the N value, chemical shifts of the α-protons were calculated in the same way from the centre of the low field multiplet. The chemical shifts of pyridine were calculated in the same way from the AA'BB'MX spectrum ($H_M = H_\gamma$) using N value of 7·0 Hz (averaged from the values of other derivatives), and J_{meta} ($J_{AM} = J_{AM'}$) of *ca.* 2 Hz. This approximate analysis is within the error of ±0·01δ.)

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