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NUCLEOPHILIC CHARACTER OF ALKYL RADICALS—X[1]

POLAR AND STERIC EFFECTS IN THE ALKYLATION OF 3-SUBSTITUTED PYRIDINES BY t-BUTYL RADICAL

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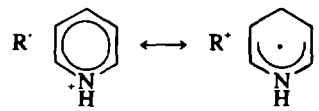
Abstract—Homolytic t-butylation of 3-substituted pyridines occurs with complete selectivity in position 6. Steric and polar effects contribute to determine the exceptional selectivity. The relative rates correlate with the Hammett σ_p constants ($\rho = 5{\cdot}5$). The results are discussed in terms of a transition state similar to a charge-transfer complex.

The great synthetic interest of the homolytic alkylation of protonated heteroaromatic bases is mainly determined by the very high positional and substrate selectivity, which was ascribed to the influence of polar effects, due to the nucleophilic character of the alkyl radicals and the electron-deficient character of the protonated heteroaromatic ring.[2] The positional selectivity is always determined by the protonated heterocyclic nitrogen: the attack exclusively takes place in α and γ positions.

The substrate selectivity is strongly affected by the nature of the heteroaromatic ring[3] and by the presence of substituents. Thus in 4-substituted pyridines the substitution exclusively occurs in position 2 and the effect of the substituents is very striking with the most selective radicals, such as t-alkyl radicals; this effect is even stronger than in classical nucleophilic substitutions.[4]

The behaviour has been interpreted on the ground of a transition state similar to a charge-transfer complex (**1**), in which a defined primary valence bond is not developed[2]



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The degree of charge development in the transition state depends on the donor character of the radical and the acceptor character of the aromatic ring, the limit case being a complete electron-transfer.†

RESULTS AND DISCUSSION

In order to have a more complete picture of the factors affecting both positional and substrate selectivity, and therefore the synthetic potential, it was necessary to investigate the effect of the substituents in position β to the heterocyclic nitrogen. Nothing of this problem was known. Pyridine substituted in position 3 was chosen as reactive model for the quantitative study.

The preliminary approach revealed considerable experimental difficulties, due to the fact that with methyl or primary alkyl radicals the non equivalent positions 2, 4 and 6 of the 3-substituted pyridines were attacked with comparable rate; the lack of attack in position 5 indicated once again that the directing effect of the protonated heterocyclic nitrogen prevailed over all the other effects. This results made the determination of the relative rates difficult by the competitive method, which required the quantitative analysis of a mixture of six compounds for each experiment, the identification of each isomer and its isolation as pure compound to check the GLC response. Previous qualitative results[5] with quinoline indicated that the reaction with a t-butyl radical could be very sensitive to steric effects. In fact the homolytic alkylation of protonated quinoline takes place with complete selectivity in 2 and 4 positions, which react with comparable reactivities with methyl, primary and secondary alkyl radicals, but not with a t-butyl radical; the latter attacks almost exclusively the 2 position of quinoline. The steric hindrance in the 4 position of quinoline is a reasonable explanation of this behaviour, because the 4 position of pyridine is more reactive than the 2 position towards a t-butyl radical.[5]

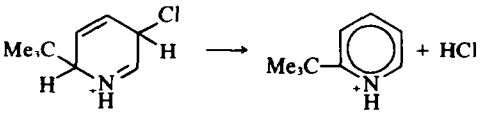
The high sensitivity to steric effects is now clearly shown by the results obtained with 3-substituted pyridines and a t-butyl radical: with all the substituents investigated only the 6 position is attacked. The 2 and 4 position, *ortho* to the substituent, are not attacked because of steric hindrance.

The very high selectivity, resulting from combined polar and steric effects, made the quantitative study easy by the competitive method.

The t-butyl radical was obtained by the silver-catalysed oxidative decarboxylation of pivalic acid by peroxydisulphate. The reaction in all cases leads to only one product, with the exception of the 3-chloropyridine, which gives the expected 2-t-butyl-5-chloropyridine (90%) and a smaller amount of 2-t-butylpyridine (10%). The

†There is some evidence of complete electron-transfer between protonated pyridines and strongly nucleophilic radicals such as $Ph_2\dot{C}$–OH (unpublished results in this Institut).

latter compound is formed, in our opinion, by loss of HCl from the dihydroderivative (2):



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2-t-Butylpyridine was included in the calculation of the relative reactivities. The relative rates are summarized in Table 1, in which are also reported for comparison the results obtained with 4-substituted pyridines and the effect of substituents in *meta* and *para* positions of a classical nucleophilic aromatic substitution. A satisfying Hammett correlation was observed with σ_p; the same correlation was not observed in the case of 4-substituted pyridines owing to an enhanced conjugation between the electron-releasing substituents and the protonated heterocyclic nitrogen.[4] The value of $\rho = 5{\cdot}5$ is of the same order of magnitude of those of nucleophilic aromatic substitutions,[6] indicating a high degree of charge development in the transition state.

Interpreting the observed selectivities in terms of polar effects, as the Hammett correlation would indicate, the more relevant characteristic of the results of Table 1 are the exceptional sensitivity to the substituent effect and the difference of selectivity determined by the substituents in *meta* and *para* positions in the homolytic t-butylation. This difference is in the expected direction, but it is too low in comparison with that of nucleophilic substitutions. We think that these results fit the mechanistic picture involving a transition state similar to a charge-transfer complex (1), as we have previously suggested. Because a primary valence bond is not developed in the transition state, the whole electron-deficiency of the pyridine ring is more important than the specific positional effect of the substituents in determining the reaction rates. The transition state of the nucleophilic substitutions, similar to a σ-complex[6] in which a primary valence bond is developed, on the contrary can be stabilized in quite a different way by a substituent depending on its *para* and *meta* position.

Table 1. Relative rates in homolytic t-butylation[a] of 3-(a)- and 4-(b)-X-substituted pyridines[4] and in nucleophilic amination of 1-Cl-2-NO_2-4-(c)- and 5-(d)-X-benzenes with piperidine[9]

X	a	b	c	d
-CN	4380	1890	5890	58·5
$-COCH_3$	956	144	—	—
$-COOC_2H_5$	509	—	922	5·3
-Cl	10·7	11·1	6·2	32·3
-H	1	1	1	1
$-CH_3$	0·2	0·15	0·15	0·86

[a] t-Butylation exclusively takes place in position 6 of 3-substituted and in position 2 of 4-substituted pyridines.

An alternative explanation of the selectivity observed, which does not involve polar effects, could be similar to that suggested by Zavitsas *et al.*[7] for the hydrogen abstraction from substituted toluenes. In our case the electron-withdrawing substituents would increase and the electron-releasing substituents would decrease the strength of the bonds formed between the alkyl radical and the pyridine ring, affecting in this way the reaction rates. There is however no evidence supporting such an interpretation; the selectivities observed with many carbon free-radicals follow often, but not always, the sequences of the expected strengths of the formed bonds.[2] Thus acyl radicals, which are expected to form weaker bonds than alkyl radicals, are much less selective than secondary and tertiary alkyl radicals.[8] Moreover carbon-free radicals with electrophilic character, due to the presence of electron-withdrawing groups, do not react at all with protonated pyridines, thus showing the importance of the polar effects.

We also think that the dissociation energy of the bond formed between the alkyl radical and the heterocyclic ring is actually an important factor responsible for the selectivity observed, but only because it contributes to determine the extent of charge-transfer in the transition state, in addition to the polarity and polarizability of the radical and the aromatic compounds. All the other conditions being equal, the lower the dissociation energy the more the transition state would be similar to the charge-transfer complex (1) according to the Hammond postulate.

In this sense the low dissociation energy expected for the bond with a t-butyl radical in comparison with primary and secondary alkyl radicals can be one of the factors contributing to determine the very high selectivity shown in Table 1.

EXPERIMENTAL

Materials. Pyridine, 3-acetyl-, 3-cyano-, 3-carboxyethyl-, 3-chloro- and 3-methylpyridines and pivalic acid were pure grade commercial samples; their purity was checked by GLC.

GLC analyses. Were performed an a Hewlett-Packard Model 5750-G using a 6 ft. 1/8" steel column packed with U.C.C.-W-982 on Chromosorb W.-A.-W.-DMCS, 80/100 mesh.

General procedure. A soln of $(NH_4)_2S_2O_8$ (0·002 mole) in water (10 ml) was added during 30 min to a stirred mixture of the two pyridines (0·04 mole), H_2SO_4 (0·05 mole), pivalic acid (0·04 mole) and $AgNO_3$ (0·0002 mole) in water (10 ml). The mixture was kept at 90° for 1 h and then made alkaline at 0°, extracted with ether and analyzed by GLC. The results are summarized in Table 1; they are the average of two or three independent reactions and agree within ±4%.

The products were prepared and characterized in the reactions with the single pyridines:

2-t-Butylpyridine obtained as a by product in the reaction with 3-chloropyridine, was identified by comparison with an authentical sample obtained by t-butylation of pyridine.

2-t-Butyl-5-chloropyridine. MS: M^+ at *m/e* 169; major peaks at *m/e* 168, 154, 127, 126, 113; NMR ($CDCl_3$): 1·32 δ (s, 9H, $3CH_3$), 7·20–7·33 δ (d, 1H, H_5), 7·48–7·62 δ (q, 1H, H_4), 8·46–8·54 δ (d, 1H, H_2).

2-t-Butyl-5-cyanopyridine. MS: M^+ at *m/e* 160; major peaks at *m/e* 159, 145, 118, 117, 104, 77; NMR ($CDCl_3$): 1·38 δ (s, 9H,

$3CH_3$), 7·43–7·57 δ (d, 1H, H_5), 7·83–7·98 δ (q, 1H, H_4), 8·78–8·85 δ (d, 1H, H_2).

2-*t*-*Butyl*-5-*acetylpyridine*. MS: M^+ at *m/e* 177; major peaks at *m/e* 176, 162, 135, 134, 121, 91; NMR ($CDCl_3$): 1·39 δ (s, 9H, $3CH_3$), 1·61 δ (s, 3H, CH_3CO), 7·38–7·54 δ (d, 1H, H_3), 8·09–8·14 δ (q, 1H, H_4), 9·08–9·16 δ (d, 1H, H_2).

2-*t*-*Butyl*-5-*carboxyethylpyridine*. MS: M^+ at *m/e* 207; major peaks at *m/e* 206, 192, 165, 164, 151, 118; NMR ($CDCl_3$): 1·20–1·60 δ [t, 12H, $1CH_3$ (CH_3CH_2OCO) and $3CH_3$ (t-bu)], 4·20–4·65 δ (q, 2H, CH_2), 7·22–7·48 δ (d, 1H, H_3), 8·10–8·30 δ (q, 1H, H_4), 9·10–9·22 δ (d, 1H, H_2).

2-*t*-*Butyl*-5-*methylpyridine*. MS: M^+ at *m/e* 149; major peaks at *m/e* 148, 134, 107, 106, 93; NMR ($CDCl_3$): 1·36 δ (s, 9H, $3CH_3$), 2·29 δ (s, 3H, CH_3), 7·16–7·50 δ (m, 2H, H_4 and H_3), 8·40 δ (s, 1H, H_2).

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