Tetrahedron. Vol. 29, pp. 2775 to 2779 Pergamon Press 1973. Printed in Great Britain

NUCLEOPHILIC CHARACTER OF ALKYL RADICALS—IX[1]

THE BENZYL RADICAL

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(*Received in the UK 2 January 1973; Accepted for publication 1 February 1973*)

Abstract—Homolytic benzylation of 4-substituted pyridines gives 1,2-diphenylethane and a benzyl-4-substituted pyridine in a ratio determined by the nature of the 4-substituents. Substituents in the benzyl radical affect its polar character, and a Hammett correlation is observed. The results are compared with those obtained for benzoyl radicals under the same conditions.

Most studies involving the benzyl radical relate its structure and reactivity to its resonance-stabilised character. A less-known quantitative aspect is its polar (i.e. nucleophilic) character and the influence which this has on its reactivity. The influence of this polar character on the reactions of the benzyl radical is now shown to be very marked, and no less than the influence of resonance stabilization.

Alkyl radicals have a clear-cut nucleophilic character, which increases from methyl to primary, secondary and tertiary alkyl radicals,[2] revealed in macroscopic form only by suitable models in which the transition state is characterized by an adequate contribution of polar forms. Interaction of a nucleophilic radical with a substrate, A, can be described either as

$$R\cdot A \leftrightarrow R^+A^{-\cdot},$$

or (if A is positively charged) as

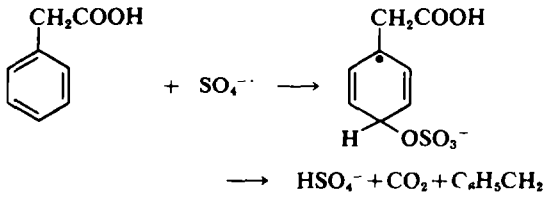
$$R\cdot A^+ \leftrightarrow R^+A^{\cdot}.$$

The stability of the cation R^+ will determine the extent to which $R^+A^{-\cdot}$, or $R^+A^{\cdot}$, contribute, an therefore the degree of nucleophilic character of the radical R. Quantitiative evaluation of the nucleophilic character of the benzyl radical, and its comparison with that of other simple carbon free radicals, is therefore of particular interest, and substituent effects in the homolytic benzylation of protonated heteroaromatic bases may be interpreted to provide this information.

RESULTS AND DISCUSSION

The silver-catalyzed decarboxylation of phenylacetic acid by peroxydisulphate was used as source of benzyl radicals. The same type of radical source had been already used to evaluate the polar character of methyl, primary, secondary and tertiary alkyl,[2] phenyl[3] and acyl[4] radicals, and allows a direct comparison to be made of the reactivity of the benzyl radical with that of ether carbon free radicals.

The oxidative decarboxylation of phenylacetic acid by peroxydisulphate has already been investigated, both in acid medium in the presence of titanous salt and at higher pH. The benzyl radical results from addition of the radical anion $SO_4^{-\cdot}$ to the aromatic ring,[5]



or through an electron transfer involving the carboxylate ion:

$$SO_4^{-\cdot} + C_6H_5CH_2COO^- \rightarrow SO_4^{--} + C_6H_5CH_2COO^{\cdot} \rightarrow CO_2 + C_6H_5CH_2^{\cdot}.$$

We believe that, in silver-catalyzed decarboxylation, the mechanism of formation of the benzyl radical is different; the benzyl radical can result from the oxidation of the carboxylic acid by the silver ion Ag^{2+} according to the following scheme:

$$S_2O_8^{2-} + Ag^+ \rightarrow SO_4^{-\cdot} + SO_4^{2-} + Ag^{2+}$$

$$SO_4^{-\cdot} + Ag^+ \rightarrow SO_4^{2-} + Ag^{2+}$$

$$C_6H_5CH_2COOH + Ag^{2+} \rightarrow C_6H_5CH_2^{\cdot} + CO_2 + H^+ + Ag^+$$

This mechanism is the same as that suggested for the aliphatic carboxylic acids,[6] but with aliphatic carboxylic acids, R—COOH, the main reaction

products are the alkane, R—H, resulting from hydrogen abstraction by the radical R·, the alkene, R(—H), and the alcohol, R—OH, deriving from the oxidation of the radical R·.[6] With phenylacetic acid, the main products resulting from radical formation are 1,2-diphenyl-ethane, from dimerization of the benzyl radical (34%), 1,2,3-triphenylpropane, from cross-dimerization of 1,2-diphenyl-ethyl radical, $C_6H_5CH—CH_2C_6H_5$ and benzyl radical (14%), benzyl alcohol (21%), and benzaldehyde, from the oxidation of the benzyl radical (31%). This different behaviour must be attributed to the resonance stabilization of the benzyl radical, the relatively high stationary concentration of benzyl radical favouring its dimerization.

The relative reaction rates of homolytic benzylation of 4-substituted-pyridines were determined by a competitive method, using an excess of heteroaromatic bases in aqueous sulphuric acid. Initially, single substrates were studied in order to observe the progress of the reaction, which in all cases is completely selective, only the α-positions of 4-substituted-pyridines being substituted by the benzyl radical. The results of relative rate studies are reported in Table 1. Some results with methyl, t-butyl and phenyl radicals, obtained under the same experimental conditions and with the same type of radical source, are also reported for comparison. The phenyl radical is the only one of the series that is not completely selective; attack at both α- and β-positions takes place consistent with the very low polar character of the phenyl radical. Benzylation of pyridine occurs appreciably only where electron-withdrawing groups are present in the pyridine ring; with pyridine itself, and in the presence of electron-releasing groups, benzylation takes place only to a small extent, and it is not possible, in these cases, to determine the relative rates of benzylation (other carbon radicals are more reactive). The ratio of benzyl-pyridines 1,2-diphenyl-ethane formed with differently-substituted pyridines, reported in Table 2, indicate that benzylation prevails with the cyano-substituent (this has a certain synthetic interest), but progressively decreases with the ester, the ketone and the chloro-derivative and becomes negligible with pyridine, and its alkyl and alkoxy derivatives. Thus the polar character of the benzyl radical determines not only the rates of benzylation in this series, but the very possibility of the reaction to occur.

Table 1. Relative rates for homolytic substitutions at position 2 in protonated 4-substituted pyridines

4-Substituent	Radical			
	Ph-CH_2	Me[2]	t-Bu[2]	Ph[3]
Cl	1·00	1·00	1·00	1·00
$COCH_3$	11·50	1·60	12·80	—
$COOC_2H_5$	28·00	—	—	—
CN	215·00	5·30	172·00	1·15

Table 2. 2-Benzyl-pyridine/1,2-diphenyl-ethane ratios in the homolytic benzylation of protonated 4-substituted pyridines

4-Substituent	2-Benzyl-pyridine (%)	1,2-Diphenyl-ethane (%)
Cl	3	97
$COCH_3$	33	67
$COOC_2H_5$	38	62
CN	98	2

A plot of $\log(K_X/K_{Cl})$ *vs.* the chemical shifts of the protons in position 2 of the protonated pyridines shows a good correlation (Fig 1). The slope of the plot (7·494) gives a measure of the selectivity of the benzyl radical. The comparison of this slope with those of methyl (2·224), n-propyl (3·014), n-butyl (3·130), sec-butyl (5·573), and t-butyl (7·455) radicals, which follow the same correlation,[2] indicates that the benzyl radical has a stronger nucleophilic character than other simple carbon radicals in homolytic aromatic substitutions. Involvement of polar forms in the transition state suggest that the ionization potentials of the radicals involved must play an important role in determining the nucleophilic character. In Fig 2, the slopes are threfore correlated with the ionization

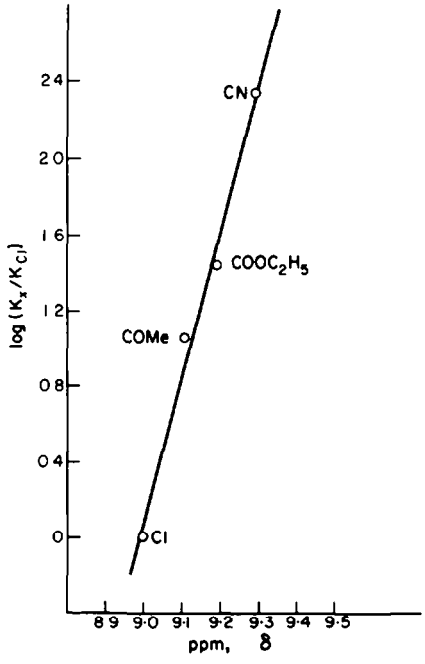


Fig 1. Correlation of relative rates of benzylation with chemical shifts of α protons in protonated 4-substituted-pyridines. Correlation coefficient: $r = 0·991$.

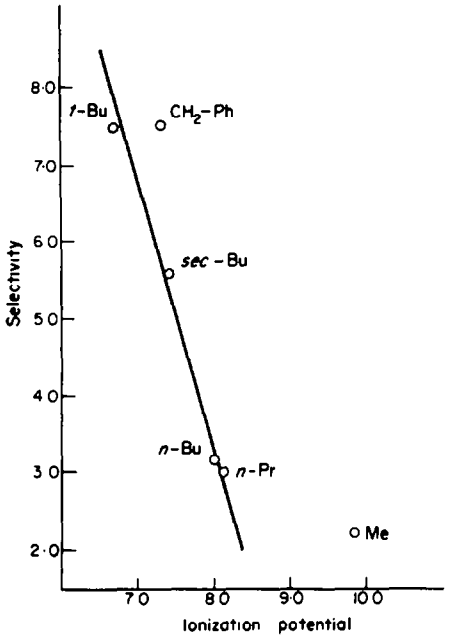


Fig 2. Correlation of the selectivity with the ionization potential.

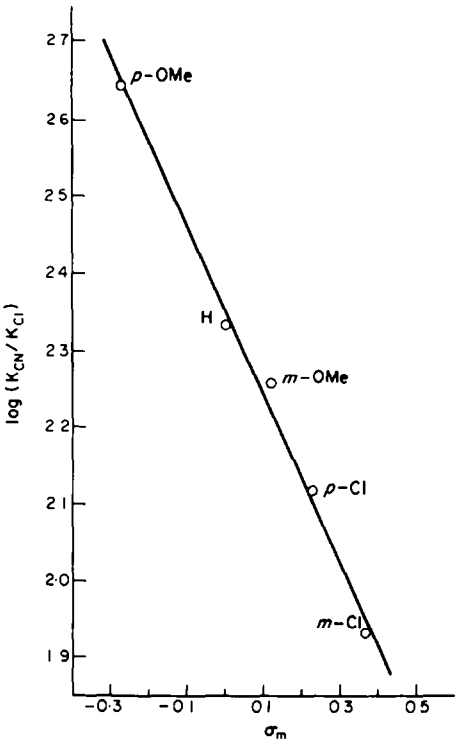


Fig 3. Correlation of relative rates of benzylation of 4-cyano- and 4-chloropyridines with σ values of substituents in the benzyl radical. Correlation coefficient: $r = 0{\cdot}996$, $\rho = -1{\cdot}09$.

potentials of the corresponding radicals; the correlation is linear for n-propyl, n-butyl, sec-butyl and t-butyl radicals but not for methyl and benzyl radicals, which are more nucleophilic than could be foreseen on the basis of their ionization potentials. Such behaviour might be attributed to the effects of solvation of the polar transition state, in the polar medium used in these studies. A higher degree of stabilization by solvation in the cases of methyl and benzyl radicals would explain the overall trend.

The rates of benzylation of 4-cyano-pyridine relative to 4-chloro-pyridine with meta- and para-substituted benzyl radical follow a Hammett correlation (Fig 3); ρ was $-1{\cdot}09$. The benzyl radical is found to be more nucleophilic than the benzoyl radical, while the acetyl radical is more nucleophilic than the ethyl radical.[4] Moreover the reactivity of benzyl radical is more strongly affected than the benzoyl radical ($\rho = -0{\cdot}49$)[4] by the presence of substituents. Different sensitivity to polar effects can be attributed to the fact that the benzyl radical is of π-type and the benzoyl radical is of σ-type.[4]

These results imply that heteroaromatic bases with positions of nucleophilic reactivity of the same order of magnitude or higher than that of the position 2 of 4-cyanopyridine are susceptible to be benzylated with good yields and very high selectivity. Thus quinoline, characterized by a more marked nucleophilic reactivity[7] than pyridine, is benzylated with high yields and complete selectivity in the positions 2 and 4 under the same experimental conditions. The ratio benzyl-quinolines/1,2-diphenyl-ethane was 90; it is higher than that for benzylation of 4-cyano-pyridine (Table 2), indicating that quinoline is more reactive than 4-cyano-pyridine; the fact was confirmed directly by determining the rates of benzylation of the position 2 and 4 of quinoline relative to the position 2 of 4-cyano-pyridine. Positions 2 and 4 of quinoline are respectively 0·44 and 2·00 times as reactive as position 2 of 4-cyano-pyridine; quinoline is therefore 1·22 times more reactive than 4-cyano-pyridine. The benzylation of quinoline was carried out both by decarboxylation of phenylacetic acid and by hydrogen abstraction from toluene by decomposition of bis(4-t-butyl-cyclohexyl)peroxy-dicarbonate. The first method was much more effective.

Lepidine gives rise to only one isomer (2-benzyl-lepidine) in this reaction, but is less reactive than quinoline; a competitive experiment shows that lepidine is 0·04 times as reactive as quinoline.

EXPERIMENTAL

Heteroaromatic compounds used as substrates were commercial products; their purity was checked by GLC. GLC analyses of the competitive reactions were performed on a Hewlett-Packard Model 5750G, using a 6 ft,

$\frac{1}{8}$" steel column, packed with 10% U.C.C. -W-982 on Chromosorb W a.w. DMCS, 80/100 mesh. The GLC analyses of benzyl-quinolines were performed on the same instrument, using a column packed with 5% XE-60 on Chromosorb W.

Decarboxylation of phenylacetic acid. A soln of $(NH_4)_2S_2O_8$ (0·05 mol) in water (20 ml) was added during 30 min to a well-stirred mixture of phenylacetic acid (0·1 mol), H_2SO_4 (0·06 mol) and $AgNO_3$ (0·005 mol) in water (20 ml) at 90°. The mixture was stirred at 90° for a further 30 min, cooled and made alkaline (NaOH) and extracted with ether. The results are reported in Table 1. The compounds were identified by comparison with authentic samples.[8]

Procedure for competitive reactions with benzyl radicals. A soln of $(NH_4)_2S_2O_8$ (0·002 mol) in water (10 ml) was added during 30 min to a well-stirred mixture of two pyridines (0·04 mol) (the pairs of pyridines and the relative molar ratios are shown in Table 3), H_2SO_4 (0·049 mol), phenylacetic acid (0·04 mol), $AgNO_3$ (0·0002 mol) in water (10 ml). The mixture was kept at 90° for 1 hr and then made alkaline at 0°, and extracted with ether. The results, summarized in Table 1, are the average of two independent reactions. The agreement between direct and calculated values in Table 3 is good; only the pair CN/Cl shows a slight discrepancy, which can be ascribed to the analytical difficulty due to the large difference of reactivity of the two substrates in the direct determination, so that the value reported in Table 1 is the average of the direct and calculated values from pairs of substrates with smaller difference of reactivity. Benzylation was also carried out under the same experimental conditions on pure 4-substituted-pyridines to observe the progress of the reaction and to establish that 2-benzyl-pyridines are the only isomers formed in all cases. Moreover, these reactions provided the ratios of benzyl-pyridines and 1,2-diphenylethane summarized in Table 2.

Table 3. Competitive benzylation of 4-substituted pyridines

4-Substituents in pairs of pyridines	Molar ratios[a]	Relative rates
CH_3CO/Cl	1:3	11·5
C_2H_5OCO/Cl	1:2	28·0
CN/Cl	1:3	205·0
$C_2H_5OCO/COCH_3$	1:1	2·4
$CN/COOC_2H_5$	1:3	8·6
$CN/COCH_3$	1:3	20·3

[a]Excess of the less reactive substrate was generally used.

The competitive reactions with meta- and para-substituted benzyl radicals were carried out by following the same procedure, i.e. by using meta- and para-substituted phenylacetic acids and a ratio 3:1 of 4-chloro- and 4-cyano-pyridine. In this case also the reactions were studied separately using the seperate substrates and selective α-substitution of the pyridine ring was established. The same procedure was used in the determination of the rate of benzylation of quinoline relative to 4-cyano-pyridine, where a ratio 1:1 of the heterocyclic substrates was used.

Mass spectra of 4 substituted-2-benzyl-pyridines show the appropriate molecular ion; a ratio 1:2 of the areas concerning the absorption peaks due to α and β aromatic protons of the pyridine ring, was observed in the NMR spectra supporting the substitution in the 2 position. The comparison with authentic samples allowed the identification of 2-benzyl-4-cyano-pyridine[9] and 2-benzyl-4-carboxyethyl-pyridine.[9] The chemical shifts of the protons in α position for protonated 4-substituted-pyridines were taken from ref. 2.

Benzylation of quinoline. (a) The reaction was carried out according to the general procedure of the competitive reactions by using different ratios of quinoline/$(NH_4)_2S_2O_8$. In all cases the product, analysed by GLC, revealed the presence of only three benzyl-derivatives; 2-benzyl-quinoline, 4-benzyl-quinoline and 2,4-dibenzyl-quinoline. The results are summarized in Table 4. 2-Benzyl-quinoline, 4-benzyl-quinoline and 2,4-dibenzyl-quinoline were identified by comparison with authentic samples.[8]

(b) A soln of quinoline (0·05 mol), trifluoroacetic acid (0·1 mol) and bis(4-t-butyl-cyclohexyl)peroxydicarbonate (0·025 mol) in toluene (50 ml) and acetic acid (40 ml) was warmed for 1 hr at 110°. After cooling, basic products were extracted into 10% aq. H_2SO_4. The aqueous soln was then made alkaline and extracted with ether. The extract was analysed by GLC; the results are reported in Table 4.

Benzylation of lepidine. The reaction was carried out as for quinoline [(a), above] by using a ratio 1:1 lepidine/$(NH_4)_2S_2O_8$. GLC analyses of the basic product revealed

Table 4. Products of benzylation of quinoline

Source of benzyl radical	Ratio quinoline/peroxide	Quinoline	2-Benzyl-quinoline	4-Benzyl-quinoline	2,4-Dibenzyl-quinoline
Phenylacetic acid + $(NH_4)_2S_2O_8$	5:1	75·7	3·8	19·8	0·7
Phenylacetic acid + $(NH_4)_2S_2O_8$	5:1·5	67·0	6·7	24·8	1·5
Phenylacetic acid + $(NH_4)_2S_2O_8$	2:1	55·0	8·3	34·2	2·5
Phenylacetic acid + $(NH_4)_2S_2O_8$	1:1	31·0	11·0	52·3	5·7
Toluene + percarbonate	2:1	76·4	9·5	14·1	trace

the presence of only lepidine (81%) and 2-benzyl-lepidine (19%). This last compound was characterized by its mass spectrum, which showed an intense molecular ion peak at $m/e = 233$ and significant peaks at $m/e = 218$, 143 and 115.

Acknowledgment—The authors thank the National Research Council (C.N.R.) for financial support.

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