Nucleophilic Character of Acyl Radicals. Substituent Effects on the Homolytic Acylation of Protonated Heteroaromatic Bases

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The relative rates of the homolytic acylation of protonated 2- and 4-substituted quinolines with acetyl and benzoyl radicals are reported. Orientation of products and reactivity show clear-cut nucleophilic character for the acyl radicals. The relative rates have not been correlated with the Hammett σ_m constants because of enhanced conjugation of the electron-releasing substituents. A much smaller effect is observed for substituted benzoyl radicals; in this case a Hammett correlation gives $\rho = -0{\cdot}49$.

THE reactions of protonated heteroaromatic bases with nucleophilic radicals such as alkyl,[1] acyl,[2] carbamoyl,[3] α-oxyalkyl,[4] and α-aminoalkyl [5] are of synthetic interest. This interest has not been extended to the same reactions with unprotonated heteroaromatic bases or with homocyclic aromatic substrates, which are not governed to a marked extent by polar factors. The quantitative evaluation of the substituent effect on reaction rates was therefore of particular interest.

RESULTS AND DISCUSSION

A particularly suitable model for the quantitative study of the homolytic alkylation of protonated heteroaromatic bases was offered by 4-substituted pyridines,[6] which are attacked by alkyl radicals exclusively at C-2. In our quantitative study of homolytic acylation by use of the same model, we met with difficulties due to the fact that the acyl group activates the pyridine ring towards further acylation so that it is difficult completely to avoid the formation of the 2,6-diacyl derivatives even with low conversion of the 4-substituted pyridine. We therefore used two analogous models with only one reactive position, the 2- and 4-substituted quinolines. Both models proved to be particularly suitable for the quantitative study of polar effects of

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substituents on the reactivity of acyl radicals for the following reasons. (*a*) The reactions are very clean and selective; only the α- or γ-positions are attacked in all cases. (*b*) The isolation and the identification of the products as well as the quantitative analysis of pairs of acyl derivatives by g.l.c. is generally easy. These characteristics are important as the relative reaction rates were determined by the competition method. (*c*) The resonance stabilization effects of the substituents are minimized, as they are in the *meta*-position with respect to the position of attack of the acyl radicals and this allows the isolation of the polar effects.

Two sources of acyl radicals were used. The first involves hydrogen abstraction from aldehydes by the redox system $Bu^tO{\cdot}OH\text{–}Fe^{2+}$ [equation (1)]. The

$$Bu^tO\cdot + RCHO \longrightarrow Bu^tOH + R\dot{C}O \quad (1)$$

second involves silver-catalysed decarboxylation of α-keto-acids with ammonium peroxydisulphate [equations (2)—(4)], a new process developed by us.[7] The acetyl

$$S_2O_8^{2-} + Ag^+ \longrightarrow SO_4^{-\cdot} + SO_4^{2-} + Ag^{2+} \quad (2)$$

$$SO_4^{-\cdot} + Ag^+ \longrightarrow SO_4^{2-} + Ag^{2+} \quad (3)$$

$$RCO{\cdot}CO_2H + Ag^{2+} \longrightarrow R\dot{C}O + CO_2 + H^+ + Ag^+ \quad (4)$$

radical from acetaldehyde and from pyruvic acid and the benzoyl radical from benzaldehyde were used. The influence of substituents in the ring of the benzoyl radical was also investigated.

To determine the relative reaction rates the competition method was used, using an excess of the heterocyclic derivative in a solution of acetic and sulphuric acid in water at 0° with the aldehyde, and in an aqueous solution of sulphuric acid at 40° with pyruvic acid. Initially single substrates were studied in order to observe the progress of the reaction. The reaction products were isolated and used to check the response of the g.l.c. analysis in the competition experiments.

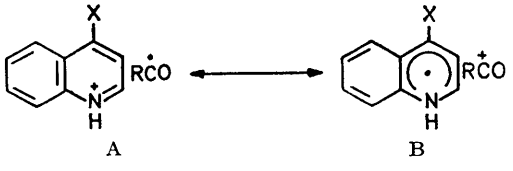
To determine the influence of substituents relative to hydrogen, quinoline was used in both series of 2- and 4-substituted quinolines; in this case small amounts (*ca.* 1% of the products) of 2,4-diacylquinoline was always formed, even if the conversion of the quinoline is very low (<5%). The relative reaction rates were therefore related to 2- and 4-methylquinolines and not to quinoline, thus avoiding in this last case the uncertainty due to the presence of 2,4-diacylquinolines. The results obtained with 4-substituted quinolines and the acetyl radical from acetaldehyde are summarized in Table 1. On the basis of orientation of products and reactivity the acetyl radical has a net nucleophilic character. 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. Such behaviour is however peculiar to the pyridine ring in reactions towards nucleophilic species (ionic and radical). It has been already observed in classical nucleophilic substitutions, such as the methoxydechlorination of 4-substituted 2-chloroquinolines,[8] 2-substituted 4-chloroquinolines,[8] 4-substituted 2-chloropyridines,[9] in the homolytic alkylation of 4-substituted pyridines with methyl,[6,10] n-propyl,[6] n-butyl,[6] s-butyl,[6] and t-butyl,[6] radicals and in the homolytic substitution at the α-position of 4-substituted quinolines with the dioxan-2-yl radical.[4] This general phenomenon can be well explained in all cases by enhanced conjugation between the electron-releasing groups X and the heterocyclic nitrogen.[8] An analogous trend was observed with the benzoyl radical and 4-substituted quinolines. The results, summarized in Table 1, show higher nucleophilic character for the benzoyl radical. This can be explained by the fact that the polar character would operate as a combination of the polar forms A and B in the transition state. The greater stability of the benzoyl ion agrees with the higher sensitivity to the polar effects of the corresponding radical. Also the influence of the substituents in the *meta*- and *para*-positions of the benzoyl radical confirms the polar character of the substituent. The rates for 4-cyanoquinoline relative to 4-chloroquinoline with *meta*- and *para*-substituted benzoyl radicals are shown in Table 2.

TABLE 1

Relative rates of acylation of 4-substituted quinolines K_X/K_{Me} [a]

Substituent, X	Acetylation: Acetaldehyde	Acetylation: Pyruvic acid	Benzoylation	δ (p.p.m.) [b]
OMe	0·032			8·88
Me	1·00	1·00	1·00	8·90
H	2·44	2·50		
Cl	4·65	4·70	4·84	9·05
CO_2Et	16·80		29·50	9·31
CN	49·50	59·00	129·9	9·41

[a] Values are the average of three independent experiments and agree to within ±4%. [b] Chemical shifts of 2-H of 4-substituted quinolines in trifluoroacetic acid.



A B

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TABLE 2

Relative rates in aroylation of 4-cyano- and 4-chloroquinoline with *meta*- and *para*-X-substituted benzaldehydes

Substituent, X	K_{CN}/K_{Cl}	Substituent, X	K_{CN}/K_{Cl}
m-Cl	16·89	H	26·82
p-Cl	19·62	*p*-Me	30·17
m-OMe	22·50	*p*-OMe	35·00

Values are the average of three independent experiments and agree to within ±3%.

observed; ρ was found to be −0·49, implying that the effect of the substituents is small; it is much smaller than the effect of substituents for heteroaromatic substrates.

The results obtained for acetyl and benzoyl radicals with 2-substituted quinolines are summarized in Table 3.

TABLE 3

Relative rates of acylation of 2-substituted quinolines with acetaldehyde and benzaldehyde

Substituent, X	K_X/K_{Me} [a]		
	Acetylation	Benzoylation	δ (p.p.m.) [b]
OMe	0·23	0·21	8·98
Me	1	1	8·99
H	2·49	2·77	
Cl	5·45	5·82	9·12
CO_2Et	11·80	24·20	9·30
CN	27·00	48·00	9·41

[a] Values are the average of three independent experiments and agree within ±5%. [b] Chemical shifts of 4-H of 2-substituted quinolines in trifluoroacetic acid.

In this case also the exclusive formation of 4-substituted products and the reactivity show clear nucleophilic character for both radicals, with greater polar character for the benzoyl radical. The behaviour is qualitatively analogous to that observed with 4-substituted quinolines. From a quantitative point of view lower sensitivity to the polar effects of substituents was observed for this series. The higher activation effect of substituents at C-4 was directly confirmed by competitive experiments with 2- and 4-cyanoquinoline. Thus 4-cyanoquinoline is 1·9 times more reactive than 2-cyanoquinoline towards the acetyl radical although C-4 of quinoline is 1·3 times more reactive than C-2. Likewise C-4 of quinoline is 2·8 times more reactive than C-2 towards the benzoyl radical, but nevertheless 4-cyanoquinoline 1·5 times more reactive than 2-cyanoquinoline.

Tables 1 and 3 give the chemical shifts of the protons at C-2 of 4-substituted and at C-4 of 2-substituted quinolines. The relative rates follow the same sequence of the chemical shifts which could mean that the major factor controlling both the relative shielding of the hydrogen nuclei *meta* to the substituent and the chemical reactivity is the electron density at C-2 of the unperturbed ground-state molecule. Table 1 also gives the results obtained from pyruvic acid and 4-substituted quinolines. The results are similar to those obtained with the acetyl radical from acetaldehyde. These results are the sole quantitative data on the substituent effect in the homolytic aromatic acylation. This effect is not known for the homocyclic series; our attempts to carry out these reactions with homocyclic substrates (benzene, anisole, 1,3-dimethoxybenzene, nitrobenzene, protonated aniline, and *NN*-dimethylaniline) were unsuccessful. The acyl radical is generally oxidized and sometimes it dimerizes rather than attacks the aromatic ring. It is clear that only aromatic substrates with very strong electron-deficient character give rise to homolytic acylation with the radical sources used by us. This fact, together with the orientation of products and the substituent effect, indicate that the course of the homolytic acylation is essentially determined by polar factors and the resonance stabilization of the intermediate radicals has a negligible importance. It is therefore interesting to compare the reactivity of the acyl radicals with that of other nucleophilic radicals, when analogous heteroaromatic substrates are used as models of the quantitative study. The relative rates of reaction of 4-substituted pyridines with methyl, n-butyl, s-butyl, and t-butyl radicals, obtained from the silver-catalysed decarboxylation of acids with peroxydisulphate,[6] are summarized in Table 4. The relative rates of the reaction of the dioxan-2-yl radical with 4-substituted quinolines[4] are summarized in Table 5.

TABLE 4

Relative rates of alkylation of 4-substituted pyridines with methyl, n-propyl, n-butyl, s-butyl, and t-butyl radicals [a]

Substituent, X	K_X/K_H				
	Me	Pr^n	Bu^n	Bu^s	Bu^t
OMe	0·27	0·12	0·10	0·02	0·0054
Me	0·53	0·35	0·32	0·28	0·15
H	1	1	1	1	1
Cl	2·38				11·12
Ac	3·60	5·57	5·60	55·60	144·00
CN	12·45	19·70	20·30	259·00	1890·00

[a] Data from ref. 6.

TABLE 5

Relative rates of dioxanylation of 4-substituted quinolines with dioxan [a]

Substituent, X	K_X/K_H	Substituent, X	K_X/K_H
OMe	0·12	Cl	2·7
Me	0·75	CO_2Et	7·1
H	1	CN	22·0

[a] Data from ref. 4.

To correlate the two series of substituted pyridines and quinolines the rates of 2- and 4-methylquinolines relative to C-2 and -4 of quinoline were determined with n-butyl, s-butyl, and t-butyl radicals; the results are shown in Table 6. Moreover the rate of acetylation of

TABLE 6

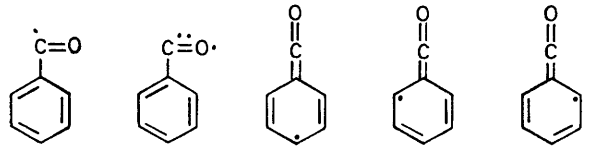
Rates for alkylation of 4-methyl- and 2-methyl-quinoline relative to C-2 and C-4 of quinoline

	Alkyl radical		
	Bu^n	Bu^s	Bu^t
$K_H/K_{Me(2)}$	2·02	4·30	
$K_H/K_{Me(4)}$		3·07	9·52
$K_{Me(2)}/K_{Me(4)}$		1·43	

The values are the average of two independent experiments and agree to within ±5%

4-cyanopyridine relative to the 4-acetylpyridine was determined; decarboxylation of pyruvic acid was used as source of the acetyl radical in order to have a direct comparison with the alkyl radicals which were also obtained by decarboxylation of acids. A value of 4·5 was obtained for low conversions in order to minimize the formation of 2,6-diacylpyridines (<1%). Analogously 4-acetylpyridine was found to be 20 times more reactive than 4-methylpyridine with the acetyl radical from acetaldehyde.[7] These data give the following sequence of nucleophilicity of the investigated radicals: methyl < primary alkyl ≃ dioxan-2-yl < acetyl < *m*-chlorobenzoyl < *p*-chlorobenzoyl < *m*-methoxybenzoyl < benzoyl < *p*-methylbenzoyl < *p*-methoxybenzoyl < s-alkyl < t-alkyl. A peculiar characteristic of this sequence is that the change of structure of the acyl radical has a small effect on its polar character. All the acyl radicals have nucleophilicities between that of a primary and a secondary alkyl radical. This is in contrast with the behaviour of the alkyl radicals, in which changes of structure causes large changes in the nucleophilic character (Tables 4 and 5).

The behaviour can be related to the structure of the acyl radicals. Stabilization of the benzoyl radical may be considered in terms of resonance structures (I)—(V).



(I) (II) (III) (IV) (V)

Thermochemical and e.s.r. data suggest that the stabilization of the benzoyl radical is solely due to a contribution from structure (II), with no contribution from structures (III)—(V). The value of 86·9 kcal mol^{-1} for the carbonyl C–H bond strength in benzaldehyde, compared with the corresponding C–H bond strengths of 87 kcal mol^{-1} in formaldehyde and in acetaldehyde,[11] indicates that there is no stabilization of the acyl radical due to substitution of a hydrogen atom by a methyl group or by a phenyl group. Also the e.s.r. spectrum [12] supports the lack of stabilization from structures (III) and (V); the major proton hyperfine splitting was due to the *meta*-hydrogen atom indicating that the benzoyl radical must be regarded as of σ-type. The radical stabilization of the benzoyl radical is therefore determined only by conjugation with the lone-pair electrons. This poor sensitivity of the character of the acyl radicals to the nature of the substituents can be compared with the small change of reactivity with changing the structure of these substituents. Also the polar character of the acyl radicals would be therefore mainly determined by the nature of the Ċ=O group and less by the substituent bonded to it. In this connection work is in progress to determine the extent of the nucleophilic character of carbamoyl, $\cdot CONH_2$, and ethoxycarbonyl, $\cdot CO_2Et$, radicals by using the same heteroaromatic models.

In conclusion the results of this work indicate that mechanisms of the homolytic acylation of protonated heteroaromatic bases, as well as that of other substitutions with nucleophilic radicals carried out by us, must be connected with the polar characteristics of the radicals and the aromatic substrates, but not with the stabilization of the intermediate radicals. This contrasts with what is known for homolytic arylation, the most studied homolytic aromatic substitution. Polar effects also play little part in the homolytic alkylation of homocyclic aromatics and unprotonated heteroaromatic bases. We [6] suggested that this contrast can be interpreted in terms of transition states, similar to a σ-complex for all kinds of homolytic arylation and in homolytic alkylation of homocyclic aromatic compounds and unprotonated heteroaromatics, and similar to a π-complex, with high contribution of polar forms, for homolytic alkylation of protonated heteroaromatic bases. We think that the results of this work support such a hypothesis for homolytic acylation also and emphasize that the models selected by us are useful for the evaluation of the relative polar character of nucleophilic radicals. The different sensitivity to the polar effects of aryl and alkyl radicals is connected, in our opinion, with the fact that the former are of the σ-type and the latter of the π-type. The acyl radicals, even if they are of σ-type, have a definite polar character because of the presence of the oxygen atom, but this polar character is little affected by substituents.

EXPERIMENTAL

N.m.r. spectra of the reaction products were recorded on a Varian A-60 spectrometer; chemical shifts are in δ p.p.m. from tetramethylsilane as the internal standard. Chemical shifts of substituted quinolines reported in Table 6 were recorded on a Varian XL-100-15 spectrometer, using a frequency counter, which provides an accuracy in locating peak positions within ±0·02 Hz. Mass spectra were obtained on a Hitachi–Perkin-Elmer RMU-6D mass spectrometer operating with an ionization energy of 70 eV. The g.l.c. analyses of the products of the competitive reactions were performed on a Varian Aerograph, Series 1200, and a Fractovap GV (Carlo Erba) equipped with a flame ionization detectors, using a column packed with 2% silicone XE-60 on silanized Gas Chrom P (80—100 mesh).

All products were separately prepared and used for determining the relative detector response in the competitive experiments. The following general procedure was used. To a solution of the substituted quinoline (0·01 mol) and aldehyde (0·1 mol), in water (15 ml), acetic acid (15 ml), and sulphuric acid (6 ml), were dropped simultaneously and separately t-butyl hydroperoxide (0·03 mol) and ferrous sulphate (0·03 mol) in water (20 ml) with stirring at room temperature. After dilution with water the acyl derivative precipitated and was purified either by crystallization or by chromatography on silica gel (hexane-ethyl acetate as eluant). No attempt was made

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to determine yields, and the reactions were carried out only to prepare pure products to use as reference samples in g.l.c.

Products.—Ethyl 2-acetylquinoline-4-carboxylate. This had m.p. 83°, *m/e* 243 (M^+), 215, and 211, δ 1·5 (t) and 4·5 (q) (Et), 2·9 (s, $COCH_3$) and 8·2 (5H, m, ArH) (Found: C, 69·2; H, 5·3; N, 5·8. $C_{14}H_{13}NO_3$ requires C, 69·1; H, 5·4; N, 5·8%).

2-Acetyl-4-methoxyquinoline. This had m.p. 96°, *m/e* 201 (M^+), 130, and 103, δ 2·8 (s, $COCH_3$), 4·1 (s, OCH_3), and 8·2 (5H, m, ArH) (Found: C, 71·7; H, 5·4; N, 6·9. $C_{12}H_{11}NO_2$ requires C, 71·6; H, 5·5; N, 7·0%).

Ethyl 2-benzoylquinoline-4-carboxylate. This had m.p. 87°, *m/e* 305 (M^+), 232, and 105, δ 1·5 (t) and 4·5 (q) (Et) and 8·0 (10H, m, ArH) (Found: C, 74·5; H, 5·0; N, 4·5. $C_{19}H_{15}NO_3$ requires C, 74·7; H, 4·9; N, 4·6%).

2-Benzoyl-4-chloroquinoline. This had m.p. 122°, *m/e* 267 (M^+), 232, and 105 (Found: C, 71·5; H, 3·8; N, 5·4. $C_{16}H_{10}ClNO$ requires C, 71·8; H, 3·7; N, 5·2%).

2-Benzoyl-4-methylquinoline. This had m.p. 109°, *m/e* 247 (M^+), 115, and 77, δ 2·8 (s, CH_3) and 8·0 (10H, m, ArH) (Found: C, 82·3; H, 5·2; N, 5·7. $C_{17}H_{13}NO$ requires C, 82·6; H, 5·3; N, 5·7%).

4-Chloro-2-(p-methoxybenzoyl)quinoline. This had m.p. 105°, *m/e* 297 (M^+), 269, and 77, δ 4·0 (s, OCH_3) and 8·0 (9H, m, ArH) (Found: C, 68·8; H, 4·2; N, 4·7. $C_{17}H_{12}ClNO_2$ requires C, 68·6; H, 4·1; N, 4·7%).

4-Chloro-2-(p-chlorobenzoyl)quinoline. This had m.p. 158°, *m/e* 302 (M^+), 273, and 139 (Found: C, 63·5; H, 3·0; N, 4·4. $C_{16}H_9Cl_2NO$ requires C, 63·8; H, 3·0; N, 4·6%).

4-Chloro-2-(m-chlorobenzoyl)quinoline. This had m.p. 135°, *m/e* 302 (M^+), 273, and 139 (Found: C, 63·7; H, 2·9; N, 4·5%).

The remaining products are known.[7]

Procedure for Competitive Reactions with Acyl Radicals from Aldehydes.—To a heteroaromatic substrate (0·01 mol) and aldehyde (0·05 mol), in water (15 ml), acetic acid (15 ml), and concentrated H_2SO_4 (6 ml), $Bu^tO{\cdot}OH$ (0·002 mol) and $FeSO_4$ (0·002 mol) in water (8 ml) were added simultaneously and separately with stirring. The mixture was basified with 10% NaOH and exhaustively extracted with ether. The extract was analysed by g.l.c., using the pure products for determining the relative detector response.

Procedure for Competitive Reactions with Acyl Radicals from Pyruvic Acid.—To a heteroaromatic substrate (0·01 mol), pyruvic acid (0·04 mol), and $AgNO_3$ (10^{-4} mol), in water (30 ml) and concentrated H_2SO_4 (6 ml), $(NH_4)_2S_2O_8$ (10^{-3} mol) in water (8 ml) was added at 40°. Stirring was continued at 40° for 1 h. The isolation and the analysis of the reaction products were carried out as previously.

Procedure for Competitive Reactions with Alkyl Radicals.—The experiments were carried out using the procedure for pyruvic acid. Valeric, 2-methylbutyric, and pivalic acid were used at 90°.

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