Electronic Configuration and Nucleophilicity of Carbon Free Radicals. α-Alkoxyalkyl, α-Alkoxycarbonyl, and Cycloalkyl Radicals

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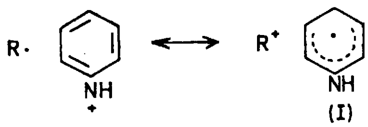
The nucleophilicity of carbon free radicals is strongly affected by the hybridization of the orbital occupied by the odd electron. An α-alkoxy-group increases the nucleophilicity of π-type alkyl radicals and decreases that of σ-type acyl radicals. The cyclopropyl radical, which has the highest *s* character, is the least nucleophilic of the cycloalkyl radicals. The general behaviour is discussed in terms of a transition state similar to a charge-transfer complex.

STRONG polar effects were recently reported in the reaction of nucleophilic carbon free radicals and protonated heteroaromatic bases.[1a–c] This behaviour has considerable synthetic and theoretical interest and has been interpreted by invoking a transition state



(1)

(I)

(I) similar to a charge-transfer complex. Such a transition state requires donor and acceptor properties of the two reagents, so that the polarity and the polarizability of both the radicals and the substrates are equally important, the stability of the pyridinyl radical (I) being a determining factor. In this respect the π or σ nature of the carbon free radicals plays an important role. Thus the behaviour of the alkyl, generally of π type, and acyl (σ type) radicals is of significance. The nucleophilicity of aliphatic and aromatic acyl radicals is intermediate between that of primary and secondary alkyl radicals,[2] *i.e.*, the acetyl radical is more nucleophilic than the ethyl radical, but the benzoyl radical is much less nucleophilic than the benzyl radical.[1b] The different polarizability of these last two radicals, due to their different configuration, was considered an important factor in this behaviour. An incipient positive charge in a transition state (I) similar to a charge-transfer complex can be stabilized in the benzyl radical by the aromatic orbitals, but not in the benzoyl radical, in which the unpaired electron occupies a hybrid orbital.[3]

A further development of quantitative relationships involving electronic configuration and nucleophilicity of alkyl and acyl radicals is now offered by the determination of polar effects in aromatic substitution with α-alkoxyalkyl, α-alkoxycarbonyl, and cycloalkyl radicals.

α-Alkoxyalkyl Radicals.—These radicals are particularly interesting because they are intermediates in most free-radical oxidations of alcohols and ethers. To investigate their nucleophilicity the effect of the substituents was determined in oxyalkylation by methoxymethyl $MeOCH_2{\cdot}$ and phenoxymethyl $PhOCH_2{\cdot}$ radicals. The radicals were produced by silver catalysed oxidative decarboxylation of methoxy- and phenoxy-acetic acid.

For both radicals and for all pyridines the reaction is completely selective, substitution taking place exclusively in position 2. The relative rates are summarized in Table 1 which also reports for comparison the corresponding values obtained with methyl and n-propyl radicals. This comparison is valid because the model reagent, the radical sources, and the experimental conditions are identical. It follows that the substitution of an α-hydrogen atom by an alkoxy-group represents a clear-cut increase of the nucleophilicity of the alkyl radicals. The cause of this increase of sensitivity to polar effects is that mentioned for the benzyl radical. α-Alkoxyalkyl radicals are of the π-type and the incipient positive charge in a transition state (I) similar to a charge-transfer complex can be stabilized by the lone-pair electrons of the oxygen atom; in terms of resonance this stabilization has the well known form (2). This electron-releasing effect

$$RO\overset{+}{C}H_2 \longleftrightarrow R\overset{+}{O}{=}CH_2 \qquad (2)$$

of the alkoxy-group overcomes the inductive electron-withdrawing effect of the same group resulting in a net increase of the nucleophilic character. The effect is more accentuated for the methoxy- than for the phenoxy-group because the methyl group induces an electron-releasing effect and the phenyl a small electron-withdrawing effect; moreover the conjugation of the lone-pair electrons of the oxygen atom with the phenyl group reduces the conjugative capacity to move resonance (2) to the right.

TABLE 1

Relative rates for homolytic substitution in the 2 position of protonated 4-X-pyridines with methoxymethyl, phenoxymethyl, methyl, and n-propyl radicals at 90°

X \ R·	$CH_3O{\cdot}\dot{C}H_2$	$PhO{\cdot}\dot{C}H_2$	$\dot{C}H_3$ [1a]	$CH_3CH_2\dot{C}H_2$ [1a]
CN	341	164	23·5	56·3
$COCH_3$	90·5	62	7	17·5
CH_3	1	1	1	1

α-Alkoxycarbonyl Radicals.—It has been recently

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[3] O. Porta, Symposium of Organic Chemistry of Italian Chemical Society, Trieste, 1973.

reported that α-alkoxycarbonyl radicals are intermediates in direct homolytic carboxylation of heteroaromatic bases.[4] Ethoxycarbonyl radicals were produced by redox decomposition by ferrous salts of the peroxide obtained from ethyl pyruvate and hydrogen peroxide. This radical source is particularly suitable because it allows work at low temperature and avoids partial hydrolysis of the esters formed in the acidic aqueous medium.

The results obtained with the same heteroaromatic substrates used for the α-alkoxyalkyl radicals are reported in Table 2. The ethoxycarbonyl radical is less nucleophilic than the acetyl radical under the same experimental conditions (from acetaldehyde, hydrogen peroxide, and ferrous sulphate at 0°); it is even less nucleophilic than the methyl radical.[1c]

In this case the unpaired electron occupies a hybrid orbital and the incipient positive charge in the transition state cannot be stabilized by the lone-pair electrons of the alkoxy-group, as with the alkoxyalkyl radical, so that only the inductive effect is working and a clear reduction in nucleophilicity is observed.

TABLE 2

Relative rates for homolytic substitution in the 2-position of protonated 4-X-pyridines with ethoxycarbonyl and acetyl radicals at 0°

X \ R·	$C_2H_5O{\cdot}\dot{C}O$	$CH_3{\cdot}\dot{C}O$ [2]
CN	18·7	
$COCH_3$	6·7	20
CH_3	1	1

The remarkable fact is therefore that the same substituent, an α-alkoxy-group, produces opposite polar effects depending on the electronic configuration of the carbon free radical.

The low nucleophilicity of the ethoxycarbonyl radical also agrees with the lower positional selectivity of substitution.[4]

Cycloalkyl Radicals.—As the nucleophilic character of acyl and alkyl radicals is due to different structural causes (mainly to the carbonyl group and to a much lesser extent to the other groups bonded to the carbonyl in acyl radicals,[2] contrary to the behaviour of the alkyl radicals), a more relevant example of the influence of hybridization on the nucleophilicity of carbon free radicals is offered by the behaviour of cycloalkyl radicals. Spectroscopic [5] and chemical evidence [6] indicates that in the cyclopropyl radical, as distinct from other cycloalkyl radicals, the unpaired electron occupies a hybrid orbital. The hyperfine coupling constants in cycloalkyl radicals are for cyclopropyl $a_{\alpha\text{-H}}$ 6·5 and $a_{\beta\text{-H}}$ 23·4 G, whereas other cycloalkyl radicals $a_{\alpha\text{-H}}$ is *ca.* 21—22 and $a_{\beta\text{-H}}$ *ca.* 35—40 G; the unusually low value of $a_{\alpha\text{-H}}$ indicates nonplanarity in the cyclopropyl radical. This suggestion is confirmed by the fact that in favourable circumstances substituted cyclopropyl radicals may undergo intermolecular reactions without loss of configurational integrity at the reaction centre.[6]

The relative rates of homolytic cycloalkylation of protonated pyridines substituted in position 4 are summarized in Table 3.

TABLE 3

Relative rates for homolytic substitutions in the 2-position of protonated 4-X-pyridines with cycloalkyl radicals

X \ R·	Cyclopropyl	Cyclobutyl	Cyclopentyl	Cyclohexyl
CN	13·9	34·2	233	256
CH_3CO	6·2	13·8	86·4	91·6
CH_3	1	1	1	1

The cyclopropyl radical is the least nucleophilic among the cycloalkyl radicals; it is even less nucleophilic than the methyl radical. Hybridization influences both polarity and polarizability of carbon free radicals because the *s*-orbitals have higher electronegativity than the *p*-orbitals; the larger the *s*-character of an orbital, the greater the electronegativity of that orbital and the lower nucleophilicity of the corresponding radical.

Another factor, also influenced by hybridization, is the strength of the bond formed between the cycloalkyl radical and the heteroaromatic ring; the greater *s*-character, the greater the bond strength. Thus we can assume that the bond formed by cyclopropyl radical is stronger than those of the other cycloalkyl radicals. According to the Hammond's postulate the transition state for cyclopropyl radical should be less like a charge-transfer complex, resulting in a reduction of the degree of charge development and therefore in lower nucleophilicity. The sensitivity to polar effects of cyclobutyl radical is intermediate between that of cyclopropyl and cyclopentyl or cyclohexyl radicals; in this case also the strength of the bond formed could be a factor influencing the transition state (the C–H bond dissociation energies in cycloalkanes [7] are: C_3 100·7, C_4 95·7, C_5 94·3, C_6 94·9 kcal mol^{-1}; the same sequence can be expected for C–C bond strengths). The same effect was considered to be one of the factors determining the very high nucleophilicity of benzyl radical.[3]

This low nucleophilicity explains the difficulty in oxidizing cyclopropyl radical by Cu^{2+}. The cyclopropyl radical is not oxidized by the same conditions under which alkyl and cycloalkyl radicals are easily oxidized by an electron-transfer process.[8] Analogous behaviour can be postulated for bridgehead radicals, such as 1-adamantyl and bicyclo[2.2.2]oct-1-yl, in which the odd electron occupies an sp^3 orbital at the bridgehead carbon atom.

As the substituent polar effects in the reactions of

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protonated heteroaromatic bases and nucleophilic radicals are sometimes of the same order of magnitude or even stronger, as for example with methoxymethyl radical, than in classical nucleophilic substitutions,[1] the question arises if this behaviour is due to the same cause or is it fortuitous. If one accepts the suggestion of a minority of interpretations,[9] according to which charge-transfer complexes play an important part in nucleophilic substitutions also, the mechanism would be practically identical; the rate-determining step between aromatic substrate and nucleophilic species would be the same, despite the radical or nonradical nature of this species. The newly emerging area in radical anion formation between aromatic compounds and nucleophiles[10] would increasingly justify the possibility of a common mechanism for substitution of some nucleophilic radicals and ionic nucleophiles.

EXPERIMENTAL

Materials.—4-Methyl, 4-acetyl-, and 4-cyano-pyridine, cycloalkylcarboxylic acids, methoxy- and phenoxy-acetic acid, and ethyl pyruvate were pure commercial samples. Purity was checked by g.l.c.

Determination of Relative Rates by a Competitive Method. General Procedure.—(a) *By oxidative decarboxylation of carboxylic acids.* This procedure was used for methoxymethylation, phenoxymethylation, and cycloalkylation. A solution of ammonium peroxydisulphate (0·002 mol) in water (10 mol) was added during 30 min to a stirred mixture of two pyridines (0·04 mol), sulphuric acid (0·05 mol), carboxylic acid (0·04 mol), and silver nitrate (0·0002 mol) in water (10 ml). The mixture was kept at 90° for 1 h and then made alkaline at 0°, extracted with ether, and analysed by g.l.c.

(b) *By redox decomposition of ethyl pyruvate peroxide.* This procedure was used for carboxylation. To a stirred solution of two pyridines (0·04 mol) and sulphuric acid (0·05 mol) in water (10 ml) were added simultaneously at 0° a solution of ethyl pyruvate (0·004 mol) in aqueous hydrogen peroxide (34%; 0·002 mol) and a solution of ferrous sulphate (0·002 mol) in water (10 ml) during 15 min. The solution was carefully basified with stirring and cooling, extracted with ether, and analysed by g.l.c.

The results are summarized in Tables 1—3. Two ratios (1 : 2 and 1 : 3) of the pairs of 4-substituted pyridines were used in competitive experiments (always with an excess of the less reactive pyridine). The values agree within ±5%. G.l.c. analyses were performed on a Hewlett–Packard model 5750 G using two 6 ft × 1/8 in steel columns packed with U.C.C.–W-982 on Chromosorb WAW-DMCS, 80—100 mesh or 10% DEGS on Chromosorb WAW-DNCS, 80–100 mesh.

Products.—The products were prepared and characterized by reactions of single pyridines. The conditions were identical with those described for competitive reactions, using a pyridine : peroxide ratio of 2 : 1 in order to minimize the formation of 2,6-disubstituted products. In all cases substitution is selective at position 2, only the carboxylation of 4-cyanopyridine giving some substitution at position 3, as previously reported.[4] Identification of products was accomplished by g.l.c.–m.s.

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