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A NEW ORTHO-EFFECT IN THE HOMOLYTIC ARYLATION OF PYRIDINE

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Molecular orbital calculations predict that when pyridine is attacked by a free radical the proportions of isomers formed will be in the order $\alpha > \beta > \gamma$[1]. This order has been observed in a number of reactions e.g. the phenylation of pyridine[2]. On the other hand, in many reactions involving attack by *ortho*-substituted phenyl radicals which have been studied qualitatively, the proportion of β-isomer formed is reported to be much higher than expected e.g. the *o*-nitrophenylation of pyridine[3]. Hey, Moulden, and Williams[4] suggested that steric effects were important in determining the isomer ratios in the reactions of *o*-substituted phenyl radicals with some monosubstituted benzenes, whereas Weingarten[5] found these to be insignificant in the Gomberg-Hey reaction. Such steric effects are expected to be, at best, minor in the arylation of pyridine (which lacks the substituent present in the studies of Hey *et al.*[4]).

We have studied quantitatively the ratios of isomers formed from some

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[1] P. Yvan, *Compt. rend.* **229**, 622(1949); R.D. Brown, *J.Chem.Soc.* 272(1956).
[2] D.H. Hey, C.J.M. Stirling, and G.H. Williams, *J.Chem.Soc.* 3963(1955).
[3] J.W. Haworth, I.M. Heilbron, and D.H. Hey, *J.Chem.Soc.* 349(1940).
[4] D.H. Hey, H.N. Moulden, and G.H. Williams, *J.ChemSoc.* 3769(1960).
[5] H. Weingarten, *J.Org.Chem.* **26**, 730(1961).

ortho-substituted phenyl radicals (from the corresponding diazonium salts) and pyridine, and compared them with those from the *para*-substituted phenyl radicals and unsubstituted phenyl itself. The diazonium salt solution was decomposed in $>$200-fold excess of pyridine at 40° ± 0.1°C, thus minimizing polyarylation, disproportionation, dimerization and the effect of the water. After concentration, the reaction mixtures were analyzed directly by vapor phase chromatography. Quantitative analyses were either carried out by VPC or by a combination of VPC and ultraviolet spectroscopy. Under these conditions, results were accurately reproducible. Total rate ratios were obtained from competitive reactions using large excesses of mixtures of benzene and pyridine in the molar ratios of 1:4, 1:5, and 1:6. Using smaller amounts of pyridine gave ${}^{py}_{C_6H_6}K$ values which were too high and not reproducible. The results are summarized in Tables I and II[6].

TABLE I

Total Rate Ratios

Radical	$C_6H_5\cdot$	*o*-CH_3-$C_6H_4\cdot$	*p*-CH_3-$C_6H_4\cdot$	*o*-NO_2-$C_6H_4\cdot$	*p*-NO_2-$C_6H_4\cdot$
${}^{py}_{C_6H_6}K$	1.14	1.72	1.44	0.47	0.78
${}^{C_6H_5NO_2}_{C_5H_6}K$[7]	2.94	--	3.4	0.26	0.94

The partial rate factors for the phenylation of pyridine differ slightly from those previously reported[2] and probably reflect the influence of the lower temperature and/or of the different arylating agent used here. It is interesting to note that 3-*o*-nitrophenylpyridine is the main isomer

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[6] All new compounds have been fully characterized.

[7] G.H. Williams, *Chem.and Ind.* 1286(1961).

formed in the ortho-nitrophenylation of pyridine (50.0% of product), in agreement with previous qualitative results[3], and contrary to the general assumption that the α-isomer is formed predominently in such reactions. The ${}^{\text{py}}_{C_6H_6}K$ values reflect the polarity of the attacking radical[7], though the spread of values is smaller than those of ${}^{C_6H_5NO_2}_{C_6H_6}K$. On the other hand, the isomer ratios are much more sensitive to the polarity of the radical in the case of pyridine. As expected, the o-tolyl radical is more nucleophilic than the p-tolyl radical, and it is confirmed that the o-nitrophenyl radical is more electrophilic than the p-nitrophenyl radical.

TABLE II

Partial Rate Factors for Arylation of Pyridine

Radical	f_α	f_β	f_γ	f_α/f_β	f_α/f_γ	f_β/f_γ
$C_6H_5\cdot$	1.83	1.00	1.18	1.83	1.57	0.86
o-$CH_3C_6H_4\cdot$	2.72	1.53	1.80	1.77	1.50	0.85
p-CH_3-$C_6H_4\cdot$	2.51	1.13	1.36	2.22	1.85	0.83
o-NO_2-$C_6H_4\cdot$	0.60	0.71	0.21	0.85	2.88	3.39
p-NO_2-$C_6H_4\cdot$	1.03	1.00	0.604	1.05	1.71	1.66

For homolytic arylations in which aroyl peroxides are used as the source of radicals Eliel, Meyerson, Welwart and Wilen[8] have suggested that the observed isomer distributions may not truly reflect whatever discrimination between positions there is in a monosubstituted benzene in the radical addition step, because of the possibility that the intermediate isomeric arylcyclohexadienyl radicals formed might undergo side-

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[8] E.L. Eliel, S. Meyerson, Z. Welwart, and S.H. Wilen, J.Am.Chem.Soc. 82, 2936(1960).

reactions at different rates. Eberhardt and Eliel[9] have further suggested that the determination of isomer ratios would give a truer picture of the reactivities of the different positions towards aryl radicals if oxygen were passed through the reaction mixture. The isomer ratios were therefore redetermined, both for the phenylation and the tolylation of pyridine, in one case with oxygen being bubbled through the reaction mixture, in a second under an atmosphere of nitrogen. Virtually no change in the isomer ratios was observed, any differences being well within the experimental error and entirely random. This might be explained either by assuming that under the present reaction conditions there is no selective removal of the isomeric aryldihydropyridyl radicals formed, or that a "cage" process is involved in which an aryl radical and a hydroxyl radical or pyridinium radical cation are generated simultaneously, the former adding to a molecule from the surrounding pyridine solvent to form the σ-complex and either of the latter abstracting a hydrogen atom from it almost immediately thereafter. After this work was completed Eliel and coworkers[10] brought forward strong evidence supporting a "cage" process in the free-radical arylations using the related N-nitrosoacetanilides.

Some interesting conclusions may be drawn when the ratios of the partial rate factors are compared. In view of the nucleophilic character of the tolyl radicals, and taking into account the susceptibility of pyridine to nucleophilic attack ($\alpha > \gamma \gg \beta$) one might expect, for instance, f_α/f_β to follow the order o-tolyl > p-tolyl > phenyl*. The observed order is p-tolyl > phenyl > o-tolyl. Similarly, the predicted order for f_α/f_γ is

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[9] M. Eberhardt and E.L. Eliel, J.Org.Chem. 27, 2289(1962).

[10] E.L. Eliel, M. Eberhardt, O. Simamura, and S. Meyerson, Tetrahedron Letters, 17, 749(1962).

* In the absence of steric effects.

o-tolyl $>$ *p*-tolyl $>$ phenyl[*]. The order found is *p*-tolyl $>$ phenyl $>$ *o*-tolyl i.e. *less α-isomer is formed than expected in the o-tolyl case*. For the nitrophenyl radicals the observed orders for f_α/f_β and f_β/f_γ are the same as those predicted on the assumption that the ease of attack at the various positions in pyridine by an electrophilic radical is in the sense $\beta > \gamma > \alpha$[11]. The expected f_α/f_γ order phenyl $>$ *p*-nitrophenyl $>$ *o*-nitrophenyl is not observed. Instead, *more α-isomer is formed with the o-nitrophenyl radical than predicted*.

These results may be rationalized by postulating a new type of "*ortho*-effect," namely:

(a) a *repulsion* between the *ortho*-methyl group and the lone pair of electrons on the pyridine nitrogen atom in the transition state leading to α-substitution[12], and

(b) an *attraction* between the *o*-nitro group in the attacking radical and the pyridine nitrogen lone pair in the corresponding transition state.

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[11] This is the order of decreasing ground-state π-electron densities. This is justified if one accepts the suggested geometry for the transition state in this type of reaction[5].

[12] D. Hofmann, E.M. Kosower, and K. Wallenfels, *J.Am.Chem.Soc.* *83*, 3314(1961), have suggested a similar non-bonded repulsion between a methyl group and a negative charge on oxygen in electronically excited states.