# Upon the Validity of Partial Rate Factors based on Isomer Distributions in the Phenylation of 4-Methylpyridine with Benzoyl Peroxide

By **Simone Vidal, Jean Court,** and **Jane-Marie Bonnier,*** Université Scientifique et Médicale de Grenoble, Laboratoire de Chimie Générale, B.P. No. 53, Centre de Tri, 38041 Grenoble–Cedex

The homolytic phenylation of 4-methylpyridine with benzoyl peroxide in refluxing benzene has been studied. The reactivities of the two nuclear positions of 4-methylpyridine towards attack by phenyl radicals depend on the benzoyl peroxide concentration used. The isomer ratio remains constant when reactions were carried out in presence of nitrobenzene. The significance of these results is discussed.

MUCH work has been done on the decomposition of aroyl peroxides in aromatic solvents. Orientation and reactivity have been determined by product analysis; orientation is given by isomer distribution, and reactivity by the ratio of arylated products formed from two competing substrates. From these results partial rate factors are calculated, giving a measure of the reactivities of the different positions in the substrate relative to the reactivity of each position in benzene. If the reaction proceeded in one step, the validity of rate factors in free radical substitution could not be contested, but as shown in Scheme 1, the reaction proceeds in two steps (b) and (c).

The validity of rate factors derived from data on isomer distribution and substrate competition has been seriously questioned on the basis of the following findings.

$$(Ar^1COO)_2 \longrightarrow Ar^1COO\cdot \longrightarrow Ar^1\cdot + CO_2 \quad (a)$$

$$Ar^1\cdot + Ar^2H \longrightarrow Ar^1Ar^2H\cdot \quad (b)$$

$$Ar^1Ar^2H\cdot + \text{oxid. agent} \longrightarrow Ar^1Ar^2 \quad (c)$$

$$2\ Ar^1Ar^2H\cdot \longrightarrow (Ar^1Ar^2H)_2 \quad (d)$$

$$2\ Ar^1Ar^2H\cdot \longrightarrow Ar^1Ar^2H_2 + Ar^1Ar^2 \quad (e)$$

$$Ar^1Ar^2H_2 + \text{oxid. agent} \longrightarrow Ar^1Ar^2 \quad (f)$$

SCHEME 1

In the thermal decomposition of benzoyl peroxide in benzene, 1,4-dihydrobiphenyl, tetrahydro-*p*-quater-

phenyl, and quaterphenyls are formed;[1-3] therefore phenylcyclohexadienyl radicals are not completely oxidised [reaction (c)] and can undergo dimerisation (d) and disproportionation (e). The presence of oxygen during aroyl peroxide decomposition in benzene increases the yield of biaryl;[4] other oxidising agents (nitrobenzene, nitrosobenzene, *etc.*) have the same effect.[5-7] Isotope effects are observed in the arylation of deuteriated benzenes.[8]

Nevertheless Morrison and Cazes[9] who studied phenylation of substituted benzenes by benzoyl peroxide in both the absence and the presence of oxygen showed that, even though biaryl yields are increased as much as threefold by oxygen, isomer distribution and relative reactivities remain unchanged. They concluded that the side reactions (d)—(f) are not selective. This conclusion does not seem to be valid in all cases. For example thermal decomposition of benzoyl peroxide in 4-methylpyridine does not give the same isomer distribution with or without oxidising agents present.[10] We also observed that in phenylation of methylpyridinium chlorides, isomer distributions and partial rate factors are drastically changed in presence of catalytic amounts of nitrosobenzene.[11]

Our purpose was to study the modifications of isomer distribution in the homolytic phenylation of 4-methylpyridine, with different oxidising agent concentrations. It is well known that the oxidising agent is mainly benzoyl peroxide itself and benzoyloxyl radicals. Therefore in order to decrease the oxidising agent concentration we added a solvent (benzene) to the mixture of 4-methylpyridine and benzoyl peroxide.

## RESULTS AND DISCUSSION

Table 1 lists isomer distributions obtained by thermal decomposition of benzoyl peroxide under various conditions. The molar ratio of benzoyl peroxide to 4-methylpyridine was maintained constant and increasing quantities of benzene were added. For each mixture the reaction was carried out with and without a small amount of nitrobenzene (an efficient oxidising agent[12,13]). Note that in the presence of nitrobenzene, the isomer distribution remains unchanged whatever the quantity of benzene. Moreover the isomer ratios of 2- and 3-phenylated methylpyridines (45 and 55%, respectively) are identical with those obtained by Abramovitch and Saha[14] under the conditions of the Gomberg–Hey reaction. The validity of isomer ratios obtained in the Gomberg–Hey arylation has been discussed[15] and the conclusion was reached that the σ complexes formed are not selectively removed by dimerisation or disproportionation. Therefore the isomer ratios observed in presence of nitrobenzene can be accepted as a measure of the relative reactivities of nuclear positions in 4-methylpyridine towards phenyl radicals.

TABLE 1

Distribution of phenylated 4-methylpyridines formed by thermal decomposition of benzoyl peroxide in presence of different additives at 80 °C for 48 h

| Experimental conditions | | Isomer distribution (%) | |
|---|---|---|---|
| Benzene (ml) added to 4-$MeC_5H_4N$ | Additive | 2- | 3- |
| None [a] | None | 53 | 47 |
| | $PhNO_2$ (1 g) | 45 | 55 |
| None [b] | None | 45 | 55 |
| | $PhNO_2$ (1 g) | 44·5 | 55·5 |
| 25 [b] | None | 51·5 | 48·5 |
| | $PhNO_2$ (1 g) | 44·7 | 55·3 |
| 50 [b] | None | 52 | 48 |
| | $PhNO_2$ (1 g) | 46 | 54 |
| 75 [b] | None | 55·5 | 44·5 |
| | $PhNO_2$ (1 g) | 45·5 | 54·5 |
| 100 [b] | None | 56 | 44 |
| | $PhNO_2$ (1 g) [c] | 44·5 | 55·5 |
| | under $N_2$ | 57 | 43 |
| 150 [b] | None | 53·3 | 46·7 |
| | $PhNO_2$ (1 g) | 45 | 55 |
| 200 [b] | None | 47 | 53 |
| | $PhNO_2$ (1 g) | 45 | 55 |
| | under $N_2$ | 62 | 38 |
| | under $O_2$ | 45 | 55 |

[a] Reactions carried out at 115° for 4 h with benzoyl peroxide to 4-methylpyridine molar ratio of 0·16. [b] Reactions carried out at 80° for 48 h with benzoyl peroxide to 4-methylpyridine molar ratio of 0·05. [c] With 0·5 g of nitrobenzene instead of 1 g the isomer distribution was 2- : 3- 50·3 : 49·7.

In the absence of additives the apparent reactivity of the 2-position increases as the amount of added benzene increases up to 100 ml. At higher dilution this reactivity surprisingly decreases; reactions were carried out in air, so we attribute this fact to oxidation by oxygen dissolved in the reaction mixture. The disproportionation, dimerisation, and oxidation reaction rates of the σ complexes are given by equations (1)—(3).

$$v_{dis} = k_1[PyrHPh\cdot]^2 \quad (1)$$

$$v_{dim} = k_2[PyrHPh\cdot]^2 \quad (2)$$

$$v_{ox} = k_3[PyrHPh\cdot][O_2] \quad (3)$$

Since the quantities of 4-methylpyridine and of benzoyl peroxide, as well as the pyridine : peroxide ratio were maintained constant when increasing amounts of benzene were added, the σ complex concentration


[1] D. F. De Tar and R. A. J. Long, *J. Amer. Chem. Soc.*, 1958, **80**, 4742.
[2] D. H. Hey, M. J. Perkins, and G. H. Williams, *J. Chem. Soc.*, 1963, 5604.
[3] D. H. Hey, M. J. Perkins, and G. H. Williams, *J. Chem. Soc.*, 1964, 3412.
[4] M. Eberhardt and E. L. Eliel, *J. Org. Chem.*, 1962, **27**, 2289.
[5] D. H. Hey, M. J. Perkins, and G. H. Williams, *Chem. and Ind.*, 1963, 83.
[6] D. H. Hey, K. S. Y. Liang, and M. J. Perkins, *Tetrahedron Letters*, 1967, 1477.
[7] C. D. Hall, *Chem. and Ind.*, 1965, 384.
[8] E. L. Eliel, S. Meyerson, Z. Welvart, and S. H. Wilen, *J. Amer. Chem. Soc.*, 1960, **82**, 2936.
[9] R. T. Morrison, J. Cazes, N. Samkoff, and C. A. Howe, *J. Amer. Chem. Soc.*, 1962, **84**, 4152.
[10] J. M. Dou, G. Vernin, and J. Metzger, *Tetrahedron Letters*, 1968, 953.
[11] J. M. Bonnier and J. Court, *Bull. Soc. chim. France*, 1972, 1834.
[12] G. R. Chalfont, D. H. Hey, K. S. Y. Liang, and M. J. Perkins, *J. Chem. Soc.* (*B*), 1971, 233.
[13] G. B. Gill and G. H. Williams, *J. Chem. Soc.* (*B*), 1966, 880.
[14] R. A. Abramovitch and M. Saha, *Canad. J. Chem.*, 1966, **44**, 1765.
[15] R. A. Abramovitch and J. G. Saha, *J. Chem. Soc.*, 1964, 2175.

[PyrHPh·] decreases, whereas the oxygen concentration remains constant. Therefore the oxidation is promoted at the expense of side-reactions. Experiments under nitrogen and under oxygen confirm this interpretation. Therefore the results reported in Table 1 show that in absence of an oxidising additive, isomer distributions obtained by thermal decomposition of benzoyl peroxide depend on the peroxide concentration used, the relative reactivities being particularly erroneous at high dilution. Note that the temperature plays a prominent part in the isomer distribution modifications. For example when the reaction is carried out at 80 °C a valid measure of the reactivities of nuclear positions in 4-methylpyridine is obtained with a molar ratio of benzoyl peroxide to 4-methylpyridine of 0·05 whereas at 115 °C benzoyl peroxide ratios as high as 0·16 give erroneous results (see Table 1). The theory of rate processes cannot explain such a shift in isomer ratio with this temperature change. Moreover when nitrobenzene is added the results obtained at 80 and 115 °C are almost identical.

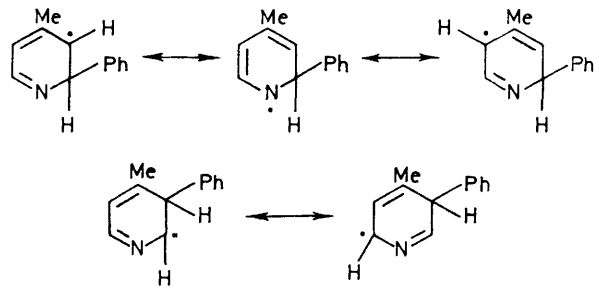
Table 2 gives the yield of 4-methyl-2-phenylpyridine, 4-methyl-3-phenylpyridine, biphenyl, and phenyl benzoate. As expected the total yield of biaryl is increased in presence of nitrobenzene.* It is important to note that the yield of 4-methyl-3-phenylpyridine is greatly increased when nitrobenzene is added whereas the yield of 4-methyl-2-phenylpyridine is almost unchanged. At high dilution the different behaviour of the two σ complexes is obvious, for example in the experiments with 100 ml of benzene the yield of 3-isomer is multiplied by a factor 1·8 while the factor for the 2-position is only 1·07. Accordingly side-reactions can be selective and the σ complexes at the 2- and 3-positions in 4-methylpyridine have different oxidation rates. In an attempt to explain this observation, we suggest that the possibility of delocalising the odd electron on the nitrogen atom might differentiate the two σ complexes (Scheme 2). According to this assumption the behaviour of the σ complex resulting from phenyl radical attack at the 3-position would be similar to that of the phenylcyclohexadienyl radical. We actually observed that nitrobenzene similarly increases the yield of 4-methyl-3-phenylpyridine and of biphenyl. However when the reactions were carried out under nitrogen, 1,4-dihydro- and 1,2-dihydro-biphenyl resulting from disproportionation of cyclohexadienyl radicals were observed as has been shown by De Tar and Long [1] but in our experiments no similar pyridine derivative could be found.

TABLE 2

Yields of products from the phenylation of 4-methylpyridine with benzoyl peroxide in refluxing benzene for 48 h

| Experimental conditions | | Yields in mole per mole of peroxide | | | |
|---|---|---|---|---|---|
| Benzene (ml) added to 4-$MeC_5H_4N$ | Additive | 4-Me-2-$PhC_5H_3N$ (× $10^2$) | 4-Me-3-$PhC_5H_3N$ (× $10^2$) | Biphenyl | Phenyl benzoate (× $10^2$) |
| None | None | 5·6 | 6·9 | | |
| | $PhNO_2$ | 4·95 | 6·05 | | |
| 25 | None | 7·25 | 6·85 | Not determined | 1·3 |
| | $PhNO_2$ | 7·5 | 9·35 | Not determined | 1·05 |
| 50 | None | 5·8 | 5·4 | 0·415 | 2·2 |
| | $PhNO_2$ | 5·5 | 6·45 | 0·48 | 1·4 |
| 75 | None | 4·3 | 3·45 | Not determined | 2·2 |
| | $PhNO_2$ | 4·15 | 4·95 | Not determined | 1·3 |
| 100 | None | 2·95 | 2·3 | 0·58 | 2 |
| | $PhNO_2$ | 3·15 | 4·0 | 0·84 | 1·45 |
| 150 [a] | None | 2·5 | 2·2 | 0·435 | 2·2 |
| | $PhNO_2$ | 2·65 | 3·3 | 0·67 | 1·9 |
| 200 [a] | None | 1·9 | 2·15 | 0·45 | 5·55 |
| | $PhNO_2$ | 2·1 | 2·55 | 0·72 | 2·85 |

[a] Reactions were carried out in presence of air; at high dilution oxygen which is present in the mixture oxidises the σ complexes (see text).



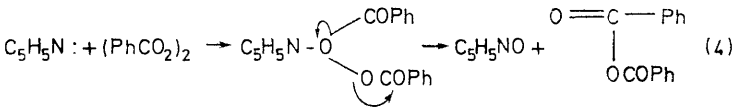

SCHEME 2

The decreased yield of phenyl benzoate which is observed in the presence of nitrobenzene was not expected. Since addition of benzoyloxyl radicals is known to be reversible, the presence of an oxidising agent would prevent the reverse reaction and therefore increase the yield of phenyl benzoate. But as has been shown previously [12] in the thermal decomposition of benzoyl peroxide in the presence of nitrobenzene a small

* This is not the case when no benzene is added although the facts that the two σ complexes have different oxidation rates and that no selective removal of the 3-isomer is observed suggest that the benzoyl peroxide concentration is large enough to oxidise the σ complexes almost completely. Therefore nitrobenzene does not increase oxidation of the complexes, but competes with methylpyridine for phenyl radicals so that the yield of methylphenylpyridines is lower.

fraction of the nitro-compound is reduced to nitrosobenzene, which scavenges phenyl radicals to form diphenyl nitroxide; the latter can interact with benzoyloxyl radicals and as a result fewer benzoyloxyl radicals react with benzene and more benzoic acid is formed.

Since benzene competes with 4-methylpyridine for phenyl radicals, the yields of 4-methylphenylpyridines should be lower when reactions are carried out in the presence of benzene than in pure 4-methylpyridine. We observed that with a benzene : 4-methylpyridine ratio of 5 the yield of 4-methylphenylpyridines is almost the same as in pure 4-methylpyridine. We attribute this observation to the fact that in pyridine derivatives a second decomposition mechanism of benzoyl peroxide competes with its homolysis. Such a possibility has been postulated by Pausacker [16] in order to rationalise the formation of pyridine oxide and the high yield of benzoic acid [17] in the thermal decomposition of benzoyl peroxide in pyridine. The proposed mechanism [equation (4)] is similar to that suggested recently [18] to




explain the accelerated decomposition of benzoyl peroxide in the presence of sulphides. We actually observed in accordance with this assumption that the yield of benzoic acid is 1·32 (in mole per mole of peroxide) in pure 4-methylpyridine whereas it is only 0·34, when benzene (200 ml) is added.

Among side-reactions cited as invalidating isomer distributions and rate factors the main ones are reactions of the cyclohexadienyl radicals which do not yield biaryls. We have shown that in the phenylation of 4-methylpyridine such reactions can be selective. We think that to avoid this source of error an efficient oxidising agent should be added to benzoyl peroxide at least in the case of pyridine derivatives.* This disagrees with the work of Morrison and Cazes [9] but is in accordance with some recent results on the reaction of benzoyl peroxide with anisole.[19] Therefore the conclusions of ref. 9 do not apply to all substrates.

* We have observed such selective side reactions in the phenylation of quinoxaline and methoxypyridines.

[16] K. H. Pausacker, *Austral. J. Chem.*, 1958, **11**, 200.
[17] D. H. Hey and E. W. Walker, *J. Chem. Soc.*, 1948, 2213.
[18] W. A. Prior and H. T. Bickley, *J. Org. Chem.*, 1972, **37**, 2885.
[19] A. McClelland, R. O. C. Norman, and C. B. Thomas, *J.C.S. Perkin I*, 1972, 570.

## EXPERIMENTAL

*General Procedure for Phenylation of 4-Methylpyridine with Benzoyl Peroxide.*—Benzoyl peroxide (1·21 g, 5 mmol) was added at 80 °C in one portion to 4-methylpyridine (9·3 g, 100 mmol) which was distilled and kept over potassium hydroxide. The mixture was stirred during 48 h at 80 °C, cooled, poured into aqueous 0·5N-sodium hydroxide (100 ml), and extracted with ether (3 × 300 ml). After drying ($Na_2SO_4$) ether was removed and the concentrated solution analysed by g.l.c.

*Reactions in the Presence of Benzene.*—The procedure was exactly the same except that benzoyl peroxide was added to a boiling solution of 4-methylpyridine (100 mmol) in thiophen-free, sodium-dry benzene (25—250 ml).

*Reactions in the Presence of Nitrobenzene.*—Nitrobenzene (1 g, 8·1 mmol) was added to 4-methylpyridine or to its solution in benzene prior to heating at 80 °C.

*Reactions under Nitrogen or Oxygen.*—Benzoyl peroxide (1·21 g, 5 mmol) was added at room temperature to a solution of 4-methylpyridine (9·3 g, 100 mmol) in benzene (200 ml) and oxygen-free nitrogen or nitrogen-free oxygen was bubbled through the mixture during 30 min at the rate of 20 ml $min^{-1}$. The mixture was then quickly brought to 80 °C and the reaction allowed to proceed during 48 h while the nitrogen or oxygen stream was maintained at the same rate.

*G.l.c. Analysis.*—For the determination of isomer ratios and yields of 4-methylphenylpyridines the conditions were: internal standard 4-phenylpyridine, column 20 ft × 3/8 in packed with 15% DEGS on 45—60 mesh Chromosorb WAW, isothermal at 200 °C, helium flow rate 300 ml $min^{-1}$. The retention times were: 4-methyl-3-phenylpyridine 39 min, 4-phenylpyridine 47 min, 4-methyl-2-phenylpyridine 57 min.

For the determination of biphenyl and phenyl benzoate the conditions were: internal standard 3-methylbiphenyl, column 6 ft × 1/4 in packed with 5% asphalt on 45—60 mesh Chromosorb G, starting temperature 150 °C, programming rate 4 °C $min^{-1}$, helium flow rate 60 ml $min^{-1}$, final temperature 200 °C.

*Product Identification.*—Each product has been identified by comparison of its i.r. spectrum with that of an authentic sample prepared according to refs. 20 and 21.

[3/1031 *Received*, 21*st May*, 1973]

[20] J. M. Bonnier and J. Court, *Bull. Soc. chim. France*, 1965, 3300.
[21] W. Huckel and R. Schewn, *Chem. Ber.*, 1956, **89**, 150.