# Isotope Effects in the *p*-Tolylation of Pyridine

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**Synopsis.** *p*-Toluoyl peroxide, *p*-iodotoluene, and di-*p*-tolyl sulfone, sulfoxide, and sulfide were photolyzed in an equimolar pyridine–pyridine-$d_5$ mixture to give rise to isomeric *p*-tolylpyridines (α, β, and γ) and their deuterated compounds. Isotopic distribution ratios ($Y_H/Y_D$) in the isomeric products were determined to be slightly larger than unity.

Vidal and coworkers[1] reported that in the phenylation of 4-methylpyridine with benzoyl peroxide (BPO), the deuterium isotope effect ($K_H/K_D$) at 2-position of the substrate was somewhat large, 3.7, though that at 3-position was 1.0. In order to check the generality of this tendency, isotope effects in arylation of pyridine with various aryl radical sources were determined. We have found previously[2] that *p*-toluoyl peroxide and *p*-iodotoluene, as well as di-*p*-tolyl sulfone, sulfoxide, and sulfide, are photolyzed in pyridine to afford isomeric *p*-tolylpyridines (α, β, and γ, respectively). Here, the isotope effects at the three nuclear positions of pyridine in the free-radical *p*-tolylation with these radical precursors were determined from the isotope distribution ratios ($Y_H/Y_D$) in the reaction products. The results are summarized in Table 1.

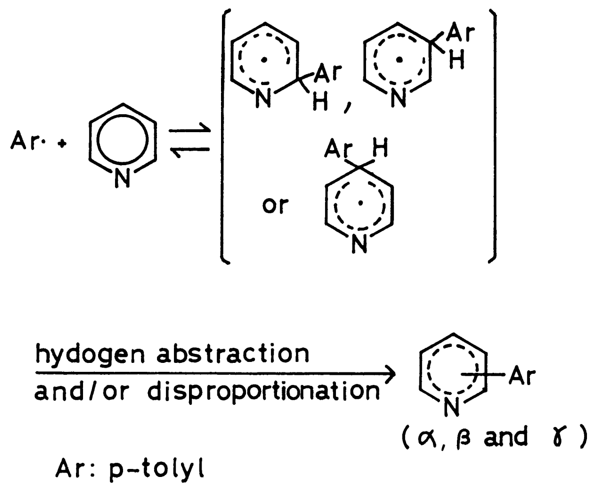
Table 1. Isotopic distribution ratios ($Y_H/Y_D$)[a)] in isomeric *p*-tolylpyridines produced in the reaction

| Run No. | Compound[b)] | *p*-Tolylpyridines α | β | γ |
|---|---|---|---|---|
| 0.015 mol dm$^{-3}$ Solution | | | | |
| 1 | $ArSO_2Ar$ | 1.06 | 1.15 | 1.09 |
| 2 | ArSOAr | 1.08 | 1.20 | 1.05 |
| 3 | ArSAr | 1.05 | 1.35 | 1.12 |
| 4 | $(ArCO_2)_2$ | 1.26 | 1.27 | 1.10 |
| 5 | ArI | 1.06 | 1.19 | 1.17 |
| 0.15 mol dm$^{-3}$ Solution | | | | |
| 1′ | $ArSO_2Ar$ | 1.09 | 1.14 | 1.08 |
| 2′ | ArSOAr | 1.05 | 1.18 | 1.07 |
| 3′ | ArSAr | 1.14 | 1.45 | 1.11 |
| 4′ | $(ArCO_2)_2$ | 1.30 | 1.30 | 1.13 |
| 5′ | ArI | 1.06 | 1.12 | 1.12 |

a) Experimental error is ±0.05. b) Ar is *p*-tolyl.

As shown in Table 1, only small isotope effects (<1.5) were observed for *p*-tolylation of all positions of pyridine; no case was found in which 2-arylation showed a larger isotope effect than 3-arylation. The difference with the result by Vidal *et al.*[1] appears to depend on the radical sources.

Eliel and coworkers[3] reported that, in the phenylation of benzene-$d_6$ with the phenyl radical generated from BPO, the isotope effects ($K_H/K_D$=1.0—6.6) vary with the concentrations of BPO used in the reaction. As Table shows, however, the values of $Y_H/Y_D$ in the present reactions were independent of the concentrations of the radical sources used under our conditions.




On the basis of the mechanism[3-5] proposed for homolytic arylations of aromatic compounds, it seems reasonable to consider that the product isotope effect is observed in either of the following cases: (1) reversal of the addition of *p*-tolyl radicals on pyridine, or (2), disproportionation and combination between *p*-tolyldihydropyridyl radicals takes place in competition with the production of the *p*-tolylpyridines. In order to check the reversibility of addition of *p*-tolyl radicals to pyridine, the peroxide and the iodide were allowed to react with a small excess of an equimolar pyridine–pyridine-$d_5$ mixture, and isotopic compositions of the recovered pyridine were compared with those of the starting one. The data in Table 2 reveal that the recovered pyridine was completely unchanged in its isotopic composition within the experimental errors. This finding implies that the values of $Y_H/Y_D$ larger slightly than unity are due to disproportionation and combination between the dihydropyridyl radicals; the disproportionation and combination compete with the hydrogen abstraction from the radical to yield the *p*-tolylpyridines.

Table 2. Isotopic compositions of starting[a)] and recovered pyridine-pyridine-$d_5$ mixture

| Run No.[b)] | Compound[c)] | Pyridine, (% in mol) | Pyridine-$d_5$, (% in mol) |
|---|---|---|---|
| 1 | $(ArCO_2)_2$ | 48.72(48.72) | 51.28(51.28) |
| 2 | ArI | 48.88(48.93) | 51.02(51.07) |

a) The figures in parentheses indicate those for starting materials. b) In run 1, refluxed for 6 h at boiling point of pyridine. c) Ar is *p*-tolyl.

Table 1 indicates that the values of $Y_H/Y_D$ change with the radical sources to some extent and that in most runs, the values of $Y_H/Y_D$ of β-(*p*-tolyl)pyridines are somewhat larger than those of α- and γ-compounds. The reason for these tendencies is not clear at present.

## Experimental

*Materials.* Commercial available di-*p*-tolyl sulfone and sulfoxide and *p*-iodotoluene were purified by recrystallization and employed for the reaction. *p*-Toluoyl peroxide and authentic *p*-tolylpyridines ($\alpha$, $\beta$, and $\gamma$) were prepared and purified by the method[2] reported previously. Di-*p*-tolyl sulfide was prepared by the literature method[6] from reduction of the corresponding sulfoxide with trichlosilane and recrystallized from ethanol (mp 58.5 °C). Pyridine–pyridine-$d_5$ (isotope purity 99%) were purchased from E. Merck, Darmstadt, and used for the reaction without further purification.

*General Procedure for Photolysis of Radical Sources in Pyridine–Pyridine-*$d_5$ *Mixture.* The procedure for the sulfone is described here as a typical run. An equimolar pyridine–pyridine-$d_5$ mixture was prepared and its isotopic content was determined by GC-MS analysis. In the case of 0.15 mol dm$^{-3}$ solution, 0.3 mmol (74.1 mg) of the sulfone was dissolved in 2 ml of the pyridine mixture. Each solution was placed in a Pyrex cylinder, degassed five times, sealed, and irradiated for 200 h at room temperature with a 400 W medium-pressure mercury arc lamp. After evaporating the excess pyridine under a reduced pressure, the residue was subjected to preparative GLC to collect a mixture of isomeric *p*-tolylpyridines produced. The preparative GLC was done on a 3 mm × 2 m stainless steel column packed with 3% OV-17 on Chromosorb GAW (DMCS), using a JEOL Chromatograph JGC-650. Three isomeric *p*-tolylpyridines were then fractionated from the mixture on a preparative HPLC with THF–hexane (1 : 9 in volume) as a solvent. The instrument used was a Waters Model 6000 A High-Pressure Liquid Chromatograph equipped with a 4 mm × 30 cm column packed with $\mu$-porasil. Each isomeric *p*-tolylpyridine thus separated was identified by comparison of its retention time with that of authentic specimen, and its deuterium content was determined by GC-MS analysis at 70 eV using a Shimadzu-LKB 9000 Gas Chromatograph-Mass Spectrometer equipped with a 3 mm × 2 m glass column packed with 0.5% OV-17 on Chromosorb GAW (DMCS). The values of $Y_H/Y_D$ of isomeric *p*-tolylpyridines were calculated from its parent peak ratios ($I_{169}/I_{173}$). The parent peak ratios were determined by repeated scans of a range of $m/e = 160$ to $m/e = 185$. It was ascertained that the parent peak ratios did not change when ionization potentials were changed from 20 to 70 eV.

*Isotopic Compositions of Starting and Recovered Pyridine–Pyridine-*$d_5$ *Mixture.* *p*-Toluoyl peroxide (1.35 g, 5 mmol) was added to an equimolar pyridine–pyridine-$d_5$ (1 g, 12.5 mmol) mixture. The mixture was refluxed at the boiling point of pyridine until evolution of $CO_2$ gas ceased. The unchanged pyridine was recovered by distillation and subjected to GC-MS analysis by using a small glass vessel in place of the OV-17 column. Its isotopic composition was calculated from the parent peak rations ($I_{79}/I_{84}$) by the technique mentioned above. *p*-Iodotoluene (2.18 g, 10 mmol) was dissolved in 1 g (12.5 mmol) of the equimolar pyridine–pyridine-$d_5$ mixture. The solution was placed in a small Pyrex cylinder, degassed, and irradiated for 200 h at room temperature with a 400 W medium-pressure mercury arc lamp. After irradiation, the unchanged pyridine was recovered by distillation and analyzed on the GC-MS. Its isotopic composition was calculated in the way described above. After irradiation for 200 h, GLC analysis indicated that 50% of the initially charged iodide remained unchanged.

## References


1) S. Vidal, J. Court, and J. M. Bonnier, *J. Chem. Soc., Perkin Trans. 2*, **1976**, 497.

2) T. Nakabayashi, T. Horii, S. Kawamura, and M. Hamada, *Bull. Chem. Soc. Jpn.*, **50**, 2491 (1977).

3) E. L. Eliel, S. Meyerson, Z. Welvart, and S. H. Wilen, *J. Am. Chem. Soc.*, **82**, 2936 (1960).

4) E. L. Eliel, Z. Welvart, and S. H. Wilen, *J. Org. Chem.*, **23**, 1821 (1958).

5) M. Kobayashi, H. Minato ,and N. Kobori, *Bull. Chem. Soc. Jpn.*, **42**, 2738 (1969).

6) T. H. Chan, A. Melnyk, and D. H. Harpp, *Tetrahedron Lett.*, **1969**, 201.