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DEUTERATION OF PYRIDINE DERIVATIVES: A VERY MILD PROCEDURE

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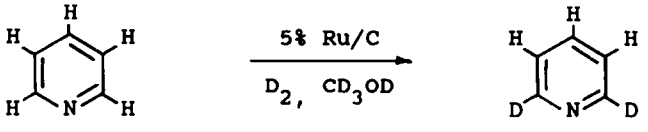
Abstract. Ruthenium on carbon selectively catalyzes the hydrogen-deuterium exchange of pyridine derivatives at the ortho position. The reaction takes place at ambient temperature under mild conditions.

Discussion

During studies using ruthenium on carbon as a heterogeneous catalyst for the hydrogenolysis of alkyl halides, it was observed that pyridine derivatives undergo alpha-hydrogen/deuterium- exchange if exposed to this catalyst in methanol-d_4, under a deuterium atmosphere at room temperature (Scheme 1).

Scheme 1



Methods for the preparation of deuterated pyridines are well known: direct H/D exchange with D_2O can be effected at 200 - 400°C,[3-5] dideutero-2,6- and trideutero-3,4,5-pyridine can be synthesized using DCl or NaOD respectively.[6] Carboxypyridines[7,8] can be decarboxylated in deuterated solvents to give the analogous deuterosubstituted species. Halogenated pyridines can be converted into the corresponding deutero adducts either by exposure to concentrated DI,[9] D_2SO_4 and zinc,[10] or by treatment with alkyllithium reagents followed by D_2O[11] or deuteromethanol.[12] Organolithium

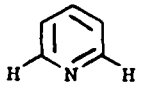
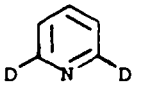
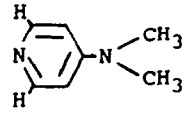
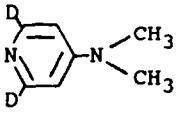
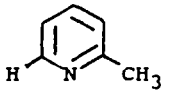
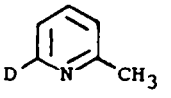
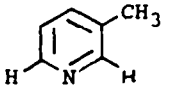
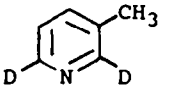
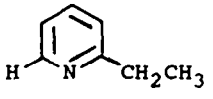
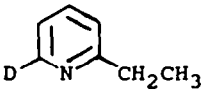
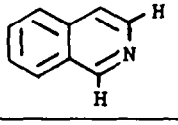
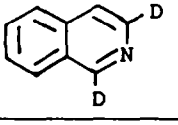
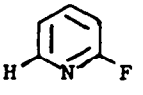
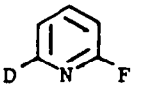
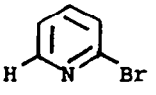
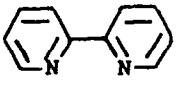
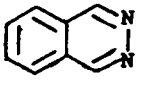
reagents can also be used to ortho-metalate aromatic oxazolines; quenching with D_2O yields selectively labeled molecules.[13]

The direct exchange of hydrogen for deuterium in the presence of a metal catalyst obviates the need for preparing specific precursors that are more complex than the desired products. A number of transition metal complexes have been reported to effect H/D exchange of aromatic hydrogens with D_2O or D_2 in homogeneous systems.[14-24] Homogeneous catalysis has been used in the regioselective deuteration of aromatic nitrogen heterocycles. Deuteration occurs at the ring positions alpha to nitrogen.[24-27] Although these methods work well they involve homogeneous catalysis which is generally more expensive and more "labor intensive" than heterogeneous catalysis.

Deuteration of pyridine derivatives by heterogeneous catalysis is also reported in the literature and shows selectivity for exchange with the hydrogens alpha to nitrogen.[24,28-31] These reactions have been carried out using Ni, Mo, Pt, Pd, Co and other metals, on a variety of supports (carbon, silica, alumina, or kieselguhr). In all cases the reaction temperatures required were 100°C or higher. The ability to effect H/D exchange at lower temperature is useful for two reasons. First, lower reaction temperatures reduce the risk of thermal decomposition and slow the rate of competing side reactions. Second, studies of several catalytic systems have shown that as the reaction temperature is increased, deuteration at the other ring positions becomes significant.[25,28,29,32] Therefore, reactions run at lower temperatures will give higher regioselectivity.

We now report results for the selective deuteration of pyridine derivatives using 5% ruthenium on carbon in methanol-d_4 under a deuterium atmosphere. All reactions were carried out at ambient temperature without pretreatment of the commercially available catalyst. Results are summarized in Table 1. The position of the incorporated deuterium was assigned by NMR (^1H, ^2H, ^{13}C as needed). Percent deuteration was calculated using NMR integration and/or mass spectral data.

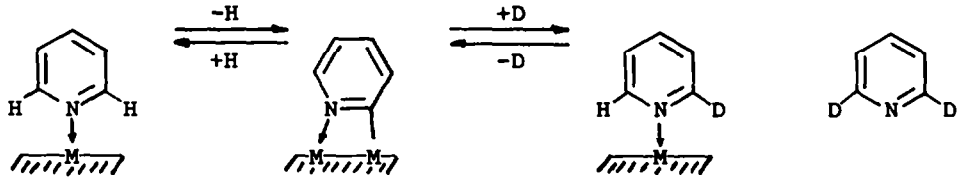
Table 1. Deuteration Study Results

Entry	Substrate	Product[a]	Comments[b]
1			no d_3 detected
2			no d_3 detected
3			7% d_2[c]
4			7% d_1[c]
5			15% d_2[c]
6			6% d_1[c] no d_3 detected
7			9% d_0[c]
8		———	no exchange
9		———	no exchange
10		———	no exchange

[a]All chemical yields are >90% as estimated by GC and/or weight of recrystallized product.
[b]No other major impurity was detected.
[c]Calculated from mass spectral data.

An examination of the data in Table 1 verifies that the yields are excellent and the transformations are regioselective when exchange occurs. The mechanism of exchange in these reactions has been a topic of much debate.[14,20,21,26,33-35] There are several possible modes of interaction between the catalyst surface and the aromatic nitrogen heterocycle.[24,27,31] It has been established in the case of pyridine that H/D exchange on metal foils takes place through the alpha-pyridyl complex, 1 (Scheme 2).[25,30,32,33,36-38]

Scheme 2



2 1 3

The alpha-pyridyl configuration confines the aromatic ring to a position perpendicular to the catalyst surface. Equilibrium is established between 1 and the lone-pair coordinated forms 2 or 3, with loss or gain of hydrogen or deuterium. Support for the premise that the nitrogen lone pair is involved with the catalyst comes from the observation that the regioselectivity of H/D exchange with toluene and pyridine are very different (pyridine exchanges at the alpha ring positions; toluene undergoes exchange with the methyl group hydrogens). However, both 2,6-dimethylpyridine, with nitrogen sterically shielded from the catalyst surface, and meta-xylene exchange at the methyl positions.[32] The nature of the metal, the type of support used,[39] the method of preparation of the catalyst and the exact structure of the substrate all play a critical role in determining the precise mechanism of the reaction. Although one must be cautious in drawing conclusions about the mechanism of one heterogeneous reaction from data derived from other systems, the

mechanism described in Scheme 2 provides a useful rationale for the results observed in this study.

The fact that coordination between the catalyst surface and the nitrogen in the aromatic ring is a favorable interaction is supported by the observation that 4-dimethylaminopyridine (entry 2, Table 1) shows selective deuteration ortho to the ring nitrogen and no N-methyl hydrogen exchange. It is well established[24,40,41] that aniline and N,N-dimethylaniline afford deuteration on the ring ortho to nitrogen rather than the methyl group. No 3,4-dideuterated products were observed in the current studies.

Both 2,2'-bipyridyl and phthalazine (entries 9 and 10) failed to exchange. These compounds have the ability to complex with the catalyst surface in two positions simultaneously, thereby preventing the formation of the requisite alpha-pyridyl complexes. This phenomenon has been described by Kishi and coworkers.[36] Using rhodium as the catalyst, pyridine was hydrogenated readily whereas 2,2'-bipyridyl did not hydrogenate without the addition of one equivalent of acid.[42] Presumably, protonation tied up the lone pair on one of the ring nitrogens which allowed for the formation of the necessary alpha-pyridyl complex.

Both 2-picoline and 2-fluoropyridine (entries 3 and 7) exchange readily whereas 2-bromopyridine (entry 8) does not exchange. Similar trends have been noted by others.[43] For instance, Garnett reported that the overall rate of H/D exchange decreased with increasing substituent size in the halobenzenes (i.e. F > Cl > Br > I).[44] The reasons for the decrease observed by Garnett are not entirely clear but could be related to the ability of the aromatic ring to adsorb to the catalyst and reduce the exchange rate at all stages of the reaction.[45]

A measurable amount of benzylic exchange was noted for 2-picoline and 2-ethylpyridine (entries 3 and 5). However, exchange at the ring positions was favored to a large extent in both cases. Isoquinoline (entry 6) has been reported to be much less reactive than either pyridine or substituted pyridines[26,30,31,46] and we noted this as well. However, if twice the usual

amount of catalyst was used and the reaction time was doubled, 1,3-dideuteroisoquinoline was obtained in excellent yield.

In summary, the current procedure affords a convenient, mild method for the preparation of specifically deuterated pyridine derivatives. Yields and ease of the procedure will hopefully recommend it for general synthetic use.

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Experimental Section

General. ^{1}H NMR spectra were recorded on a JEOL FX90Q spectrometer; reported chemical shifts are in ppm (δ) relative to $CHCl_3$ (δ 7.26). MS and GC/MS measurements were made with a VG 7070HS mass spectrometer coupled to a Hewlett-Packard model 5880A gas chromatograph. Melting points were obtained on a Thomas- Hoover apparatus and were corrected. Spectrophotometeric grade methanol was used for all washings. Methanol-d_4 was obtained in sealed 1 g glass ampules from MSD Isotopes. Each reaction was run in duplicate, and methanol-d_4 with a different lot number was used in the duplication of each run. Dry ruthenium on carbon (5%) was obtained from Aldrich Chemical Co. Inc, Milwaukee, WI. Deuterium gas was obtained in lecture bottles from Matheson Gas Products, Newark, CA. Pressure bottles were sealed with a four-holed cap over a rubber septum using a commercial bottle capper. All reactions were run in duplicate. Reference spectra were run on the same batch of purified substrate that was used in the exchange reactions.

General procedure for the deuteration of solid aromatic amines. A sealed 20 mL pressure bottle containing 0.010 g of 5% Ru-C, 0.50 mmole of the purified amine, and a magnetic stir bar was evacuated (0.100 mm Hg) and then filled with D_2 at 22 psi. After three evacuation/fill cycles, the bottle was vented to 1 atm through an argon line. Methanol-d_4 (1 g) was added via cannula. The bottle was pressurized to 22 psi of D_2, and the reaction was stirred at room temperature for 24 ± 1 h using a Corning PC-351 Hot Plate Stirrer at a setting of "5". After stirring, the bottle was vented to

atmospheric pressure with a needle through the septum. The cap was removed, and the mixture was suction filtered through a small plug (ca. 0.2 g) of moistened (MeOH) celite over a medium porosity glass fritted funnel. The remaining residue was washed out of the reaction vessel and onto the celite with four 5 mL portions of methanol. The solvent was removed under reduced pressure and the solid recrystallized prior to analysis.

General procedure for the deuteration of liquid amines. Exchange reactions were carried out using identical procedures as with solid substrates, with the exception that the liquid amine (0.50 mmol, distilled) was added using a 100 μL syringe after flushing with D_2. After stirring, the bottle was vented to atmospheric pressure with a needle through the septum. The cap was removed and the reaction mixture was suction filtered through a small plug (ca. 0.2 g) of moistened (MeOH) celite over a medium porosity glass fritted funnel (with 2-fluoropyridine, the reaction mixture was filtered directly through the glass frit without the aid of celite). The remaining residue was washed out of the reaction vessel and onto the celite with four consecutive 5 mL washings of methanol. In cases where the boiling point of the amine was too low to remove solvent prior to spectral analysis, $CDCl_3$ was used in place of methanol. Analysis was carried out without purification of the amine. In cases where the amine had a boiling point high enough to allow the solvent to be safely removed, the amine was introduced into the mass spectrometer via direct insertion. When the amine had a boiling point low enough to warrant concern, GC/MS analysis was carried out on the solution without prior removal of the solvent. NMR and MS analyses were carried out without further purification.

Spectral Data

Control experiment using 4-dimethylaminopyridine (DMAP) without catalyst. Recrystallized from hexane; mp 112-112.5°C: ^1H NMR ($CDCl_3$) δ 8.18 (d, 2H), 6.48 (d, 2H), 2.99 (s, 6H); MS, m/z (relative intensity) 122 (M^+, 80.1), 121 (100). Reference DMAP-d_0: mp 112-112.5°C; ^1H NMR ($CDCl_3$) δ 8.20 (d, 2H), 6.45 (d, 2H), 2.99 (s, 6H); MS, m/z (relative intensity) 122 (M^+, 79.6), 121 (100)

2,6-Dideutero-pyridine. H NMR ($CDCl_3$) δ 6.95-7.49 (m); GC/MS, m/z (relative intensity) 81 (M^+-d_2, 100), 80 (20.1). Reference-d_0: ^1H NMR ($CDCl_3$) δ 8.28-8.33 (m, 2H), 6.93-7.41 (m, 3H); MS, m/z (relative intensity) 79 (M^+, 100), 78 (11.7).

2,6-Dideutero-p-dimethylaminopyridine. Recrystallized from hexane mp 111-111.5°C: ^1H NMR ($CDCl_3$) δ 6.50 (s, 2H), 2.99 (s, 6H); MS, m/z (relative intensity) 124 (M^+-d_2, 74.8), 123 (100). Reference-d_0: mp 111.5-112.5°C; ^1H NMR ($CDCl_3$) δ 8.20 (d, 2H), 6.45 (d, 2H), 2.99 (s, 6H); MS, m/z (relative intensity) 122 (M^+, 79.6), 121(100).

1,3-Dideutero-isoquinoline. After 24 hours with 0.010 g of catalyst: ^1H NMR ($CDCl_3$) δ 9.19 (trace), 8.47 (trace), 7.42-7.93 (m); MS, m/z (relative intensity) 131 (M^+-d_2, 74.3), 130 (100), 129 (70.3). After 48 hours with 0.020 g of catalyst: ^1H NMR ($CDCl_3$) δ 9.01 (trace, 0.08H), 8.28 (d, 0.1H), 7.31-7.76 (m, 5H); GC/MS, m/z (relative intensity) 131 (M^+-d_2, 100), 130 (25.2), 129 (8.8). Reference-d_0: ^1H NMR ($CDCl_3$) δ 9.24 (s, 1H), 8.51 (d, 1H), 7.53-8.00 (m, 5H); MS, m/z (relative intensity) 129 (M^+, 100), 128 (17.1).

6-Deutero-2-methylpyridine. ^1H NMR ($CDCl_3$) δ 7.55 (t, 1H), 7.00-7.20 (m, 2H), 2.54 (s, 3H); MS, m/z (relative intensity) 94 (M^+-d_2, 100), 93 (24.5), 79 (18.2), 67 (34.3). Reference-d_0: ^1H NMR ($CDCl_3$) δ 8.47 (d, 1H), 7.55 (dt, 1H), 6.95-7.20 (m, 2H), 2.50 (s, 3H); MS, m/z (relative intensity) 93 (M^+, 100), 92 (20.8), 78 (17.8), 66 (45.1).

2,6-Dideutero-3-methylpyridine. After 24 hours with 0.010 g of catalyst: ^1H NMR ($CDCl_3$) δ 8.39 (trace), 7.45 (d, 1H), 7.15 (d, 1H), 2.28 (s, 3H); GC/MS, m/z (relative intensity) 95 (M^+-d_2, 100), 94 (40.6), 93 (11.4), 80 (3.8). After 48 hours with 0.010 g of catalyst: ^1H NMR ($CDCl_3$) δ 8.39 (trace, 0.2H), 7.48 (d, 1H), 7.15 (d, 1H), 2.32 (s, 3H); GC/MS, m/z (relative intensity) 95 (M^+-d_2, 100), 94 (41.2), 80 (1.98). Reference-d_0: ^1H NMR ($CDCl_3$) δ 8.40 (m, 2H), 7.48 (d, 1H), 7.17-7.22 (m, 1H), 2.31 (s, 3H); MS, m/z (relative intensity) 93 (M^+, 100), 92 (31.5), 78 (3.1).

6-Deutero-2-ethylpyridine. ^1H NMR ($CDCl_3$) δ 7.50 (t, 1H), 7.00-7.20 (m, 2H), 2.80 (q, 2H), 1.26 (t, 3H); GC/MS, m/z (relative intensity) 108 (M^+-d_1,

64.3), 107 (100), 80 (33.5). Reference-d_0: H NMR ($CDCl_3$) δ 8.50 (d, 1H), 7.55 (dt, 1H), 6.85- 7.15 (m, 2H), 2.79 (q, 2H), 1.25 (t, 3H); MS, m/z (relative intensity) 107 (M^+, 50.8), 106 (100), 79 (30.8).

6-Deutero-2-fluoropyridine. ^1H NMR ($CDCl_3$) δ 7.80 (dd, 1H), 7.15 (d, 1H), 6.90 (dd, 1H); MS, m/z (relative intensity) 98 (M^+- d_1, 100), 97 (8.0). Reference-d_0: ^1H NMR ($CDCl_3$) δ 8.20 (d, 1H), 7.80-7.91 (m, 1H), 6.80-7.30 (m, 2H); MS, m/z (relative intensity) 97 (M^+, 100), 96 (8.0).

References

1. Present address: Chemistry Division, National Science Foundation, Washington, D.C. 20550
2. Present address: Research and Development, Baker Performance Chemicals, Inc. 3920 Essex Lane, Houston, TX 77027
3. Werstuik, N. H.; Ju, C. Can. J. Chem. **1989**, 67, 5.
4. Zoltewicz, J. A.; Meyer, J. D. Tetrahedron Lett. **1968**, No. 4, 421.
5. Werstuik, N. H.; Kadai, T. U.S. Patent 3 989 705 **1976**.
6. Zoltewicz, J. A.; Smith, C. L. J. Am. Chem. Soc. **1967**, 89, 3358.
7. Zoltewicz, J. A.; Smith, C. L.; Meyer, J. D. Tetrahedron **1968**, 24, 2269.
8. Mauzerall, D.; Westheimer, F. H. J. Am. Chem. Soc. **1955**, 77, 2261.
9. Zoltewicz, J. A.; Smith, C. L. J. Am. Chem. Soc. **1966**, 88, 4766.
10. Bak, B.; Hansen, L.; Rastrup-Anderson, J. J. Chem. Phys. **1954**, 22, 2013.
11. Abramovitch, R. A.; Kroeger, D. J.; Staskun, B. Can. J. Chem. **1962**, 40, 2030.
12. Verbeek, J.; George, A. V. E.; deJong, R. L. P.; Brandsma, L. J. Chem. Soc., Chem. Commun. **1984**, No. 4, 257.
13. Meyers, A. I.; Mihelich, E. D. J. Org. Chem. **1975**, 40, 3158.
14. Lebrilla, C. B.; Maier, W. F. J. Am. Chem. Soc. **1986**, 108, 1606.
15. Lewis, L. N. Inorg. Chem. **1985**, 24, 4433.
16. Lockley, W. J. S. J. Labelled Comp. Radiopharm. **1983**, 21, 45.
17. Lockley, W. J. S. Tetrahedron Lett. **1982**, 3819.
18. Parshall, G. W. Acc. Chem. Res. **1975**, 8, 113.
19. Herbert, R. B. Tetrahedron Lett. **1973**, 1375.
20. Fraser, R. R.; Renaud, R. N. J. Am. Chem. Soc. **1966**, 88, 4365.

21. Garnett, J. L.; Sollich, W. A. Aust. J. Chem. 1965, 18, 1003.

22. Crawford, E.; Kemball, C. Faraday Soc. Trans. 1962, 58, 2452.

23. Constable, E. C. J. Chem. Soc., Dalton Trans. 1985, No.12, 2687.

24. Garnett, J. L.; Henderson, L. J.; Sollich, W. A.; Tiers, G. V. D. Tetrahedron Lett. 1961, 516.

25. Moyes, R. B.; Wells, P. B. J. Catal. 1971, 21, 86.

26. Calf, G. E.; Garnett, J. L.; Pickles, V. A. Aust. J. Chem. 1968, 21, 961.

27. Garnett, J. L.; Sollich, W. A. Aust. J. Chem. 1962, 15, 56.

28. Sonnemans, J.; Janus, J. M.; Mars, P. J. Phys Chem. 1976, 80, 2107.

29. Fransen, T.; van der Meer, O.; Mars, P. J. Phys Chem. 1976, 80, 2103.

30. Calf, G. E.; Garnett, J. L. J. Chem. Soc., Chem. Commun. 1967, 7, 306.

31. MacDonald, C. G.; Shannon, J. S. Tetrahedron Lett. 1964, 3351.

32. Wexler, R. M.; Muetterties, E. L. J. Am. Chem. Soc. 1984, 106, 4810.

33. Wexler, R. M.; Tsai, M-C.; Friend, C. M.; Muetterties, E. L. J. Am. Chem. Soc. 1982, 104, 2034.

34. Thomas, A. F. Deuterium Labeling in Organic Chemistry; Meredith Corporation: New York, 1971; pp 290-338.

35. Ozaki, A. Isotope Studies of Heterogeneous Catalysis; Academic Press: New York, 1977.

36. Kishi, K.; Ikeda, S. J. Phys Chem. 1969, 73, 2559.

37. Kishi, K.; Chinomi, K.; Inoue, Y.; Ikeda, S. J. Catal. 1979, 60, 228.

38. Morrow, B. A.; Cody, I. A.; Moran, L. E.; Palepu, R. J. Catal. 1976, 44, 467.

39. Hightower, J. W.; Kemball, C. J. Catal. 1965, 4, 363.

40. MacDonald, C. G.; Shannon, J. S. Aust. J. Chem. 1967, 20, 297.

41. Lauer, W. M.; Errede, L. A. J. Am. Chem. Soc. 1954, 76, 5162.

42. Freifelder, M. Adv. Catal. Relat. Subj. 1963, 14, 203; and references therein.

43. MacDonald, C. G.; Shannon, J. S. Aust. J. Chem. 1965, 18, 1009.

44. Garnett, J. L.; Sollich, W. A. Aust. J. Chem. 1961, 14, 441.

45. Harper, R. J.; Kemball, C. Faraday Soc. Trans. 1969, 65, 2224.

46. Ashby, R. A.; Garnett, J. L. Aust. J. Chem. 1963, 16, 549.