Intramolecular kinetic isotope effect in hydride transfer from dihydroacridine to a quinolinium ion. Rejection of a proposed two-step mechanism with a kinetically significant intermediate

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SUPPORTING INFORMATION

10-Methylacridinium iodide. 10-Methylacridinium iodide was prepared from acridine and fourfold excess of methyl iodide in a minimum amount of acetone. The solution was sealed and maintained at room temperature for 2 weeks, during which time the product separated as a crystalline solid. The material was carried on without further purification. (80%. yield), mp 231-232 ºC (lit.[1] 228-230); ^{1}H NMR (400 MHz, DMSO-d_6), δ 4.846 (3H, s), 8.0480 (2H, t, J = 7.2 Hz), 8.436-8.476 (2H, t, J = 6.8 Hz), 8.618-8.649 (2H, d, J = 12.4 Hz), 8.774-8.797 (2H, d, J = 9.2 Hz), 10.192 (1H, s).

10-Methyl-9,10-dihydroacridine-9-*d*. 10-Methylacridium iodide (0.7 g, 2.2 mmol) was dissolved in 40mL of a 2:1 methanol-water mixture and cooled to 10 ºC. To this solution 100mg (2.5 mmol) of $NaBD_4$ (Cambridge Isotope Labs, Inc.) dissolved in 3ml of water was added dropwise. The product separated promptly and spontaneously. To decrease the solubility of the product in the solvent, an additional 40ml of water was added. Four 10-mL portions of dichlormethane were used to extract the product from the aqueous mixture. The dichloromethane was removed under vacuum at 40 ºC. The resulting solid was purified by recrystallization from absolute ethanol and kept under nitrogen and stored in a refrigerator, to protect it from air oxidation. (80%), mp 92-93 ºC (lit.[2] 93-5ºC, undeuterated); ^{1}H NMR (400 MHz, CD_3CN), δ 3.378 (3H, s), 3.847 (1H, s), 3.874 (0.13H, s), 6.918-6.985 (4H, m), 7.187-7.247 (4H, m). The ^{1}H NMR spectrum shows an integration of 1:22.7 for the signals at δ-3.874 and 3.847. This corresponds to a ratio of 1:45.4 of 10-methyl-9,10-dihydroacridine to 10-methyl-9,10-

dihydroacridine-9-*d*, or 2.2% undeuterated 10-methyl-9,10-dihydroacridine, which arises because the reagent $NaBD_4$ is only 98.9% deuterated.

1-Benzyl-3-cyanoquinolinium perchlorate. 1-Benzyl-3-cyanoquinolinium bromide was prepared by refluxing 3-cyanoquinoline with 4 equivalents of benzyl bromide at 130-140 ºC for 2-3 hours.[3] The reaction mixture was cooled to room temperature and the resulting precipitate was collected by suction filtration and washed several times with chloroform. The green solid was carried on to further synthesis without purification: (75%), mp 183.5-184.7 ºC (lit[4] 185ºC); ^{1}H NMR (400 MHz, DMSO-d_6), δ 6.405 (2H, s), 7.38 (3H, m), 7.50 (2H, m), 8.14 (1H, t, *J* = 7.6 Hz), 8.35 (1H, t, *J* = 7.2 Hz), 8.53 (2H, m), 10.02 (1H, s), 10.43 (1H, s).

To increase solubility in acetonitrile, the bromide was converted to the perchlorate by ion exchange.[5] The bromide was dissolved in dry acetonitrile in the presence of a 50-fold excess of sodium perchlorate. Solvent was evaporated to dryness, and the resulting solids were washed with water to remove all the sodium salts. The product was collected by filtration and recrystallized from absolute ethanol: (70%); mp 199-201 ºC, lit.[6] 202 C); ^{1}H NMR (400 MHz), δ 6.22 (2H, s), 7.42 (2H, m), 7.47 (3H, m), 8.14 (1H, t, *J* = 7.2 Hz) 8.36 (1H, t, *J* = 7.3 Hz), 8.48 (2H, t, *J* = 6.8 Hz), 9.53 (1H, d, *J* = 1.2), 9.59 (1H, s).

Measurement of Kinetic Isotope Effect. The hydride (deuteride) transfer reaction between 10-methyl-9,10-dihydroacridine-9-*d* (**1**-*d*) and 1-benzyl-3-cyanoquinolinium (**2**) perchlorate was carried out in acetonitrile under a narrow variety of conditions. A 1.2-1.3-fold excess of dihydroacridine over quinolinium ion was generally used in order to favor conversion to dihydroquinoline product (**3**-h_2 + **3**-*d*). The extent of reaction was monitored by TLC, with 5% ethyl acetate in hexane as elution solvent. The reaction was carried out to approximately one half-life, calculated for these concentrations according to the published rate constant and activation energy.[5,6] After an appropriate time had elapsed, ~20 mL of ether was added and the solution was extracted with 15-mL portions of water to removed unreacted 1-benzyl-3-cyanoquinolinium perchlorate, as well as the 10-methylacridinium perchlorate, the product from oxidation of 10-methyl-9,10-dihydroacridine. The solvent was evaporated from the organic layer

under gentle vacuum. The extent of reaction after 32 min could be confirmed by a ^{1}H NMR spectrum of this material, showing nearly equal amounts of 1-benzyl-3-cyano-1,4-dihydroquinoline product and unreacted 10-methyl-9,10-dihydroacridine, which had undergone no detectable change in deuterium content. The product was then purified by flash column chromatography on silica gel and eluted with 5 to 10% EtOAc in hexane. Unreacted 10-methyl-9,10-dihydroacridine-9-*d* was separated and was found to be identical to the starting material by TLC, mp, and NMR.

1-Benzyl-3-cyano-1,4-dihydroquinoline. The desired product, a mixture of 1-benzyl-3-cyano-1,4-dihydroquinoline (**3**-h_2) and 1-benzyl-3-cyano-1,4-dihydroquinoline-4-*d* (**3-*d*),** was then purified by recrystallization from absolute ethanol. The recovery, based on 1-benzyl-3-cyanoquinolinium perchlorate, was ~20%, after chromatography and recrystallization, which was sufficient for isotopic analysis. The white crystalline product was kept under nitrogen and stored in the refrigerator: mp 138-140 ºC; ^{1}H NMR (500 MHz, CD_3CN), δ 3.711 (br,t), 3.732 (s), 4.76 (2H, s), 6.67-6.68 (2H, d, J = 8 Hz), 6.88 (1H, t, J = 7.5 Hz), 6.956 (2H, t, J = 9.5 Hz), 7.05 (1H, s), 7.27-7.34 (5H, m), MS (**3**): m/z 245.12 (51%), 246.13 (11), 247.20 (32, M+H$^+$), 248.18 (6), 263.83 (100, M+NH_4^+), 264.90 (18).

Isotopic analysis. Isotopic analyses of 1-benzyl-3-cyano-1,4-dihydroquinoline (**3**) were performed by both ^{1}H-NMR in CD_3CN or $CDCl_3$ and mass spectrometry. An isotope shift leads to distinct C4 signals for CH_2 and CHD. The former appears as a singlet at δ 3.732, and the latter as a broadened 1:1:1 triplet at δ 3.711, owing to spin-spin coupling to the D. The CHD intensity can be compared to that of CH_2 by integration, but it was necessary to use 45º pulses and delay times that ensured sufficient spin-lattice relaxation of the CHD fragment. However, because the CHD signal is broader and weaker, its integration is somewhat sensitive to the range of chemical shifts assigned to it. Therefore the NMR analysis was confirmed by mass-spectrometric analysis. The deuterium content of **3** was obtained from the summed intensities of [M+H$^+$] = 247 and [M+H$^+$-2] = 245 peaks, compared to [M+H$^+$+1] = 248 and [M+H$^+$-1] = 246. The intensities were summed because M-2 peaks are enhanced in the undeuterated material.

In one case the [M+NH_4^+] and [M+NH_4^++1] intensities were found to be more reliable. In order to correct for the natural abundance of ^{13}C the mass spectrum of the **3-*d*** sample was compared with that of **3**-h_2 alone, obtained from **1** + **2**. From replicates the mass-spectroscopic [**3**-h_2]/[**3-*d***] ratio has an accuracy of ±0.15.

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