

Arenium Acid Catalyzed Deuteration of Aromatic Hydrocarbons

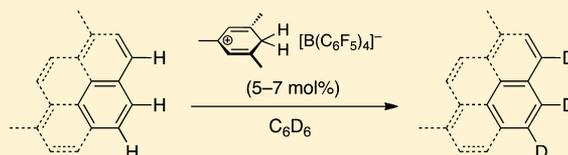
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S Supporting Information

ABSTRACT: The arenium acid [mesitylene-H]⁺ has been shown to be an extraordinarily active H/D exchange catalyst for the perdeuteration of polycyclic aromatic hydrocarbons. The reactions take place under ambient conditions in C₆D₆ as an inexpensive deuterium source. High isolated yields and excellent degrees of deuterium incorporation were achieved using the substrates *p*-terphenyl, fluoranthene, pyrene, triphenylene, and corannulene.



The demand for isotopically labeled compounds for pharmaceutical, medical, and spectroscopic applications has led to an increasing interest in the preparation of deuterated organic molecules.¹ Labeling is usually performed by H/D exchange reactions using a deuterated solvent as the deuterium source.² Many procedures have been developed to effect incorporation of deuterium into aromatic substrates; however, most of them require forcing conditions (high temperatures and pressures, strongly nucleophilic or Lewis acidic additives) and/or the use of expensive transition metals.^{3–8} Here we report on the efficient perdeuteration of polycyclic aromatic compounds using an arenium acid catalyst in C₆D₆ under ambient conditions.

The concept of pairing a cationic proton donor with a weakly coordinating anion has enabled the development of strong Brønsted acids that lack the nucleophilic and oxidative properties of traditionally used reagents such as H₃PO₄, H₂SO₄, or HClO₄.⁹ Protonated benzene derivatives can be isolated as thermally stable carborane and tetraarylborate salts.^{10,11} In these arenium acids, vast protonation power is decoupled from destructive oxidation chemistry. Such clean Brønsted acid character evokes a procedure that uses an arenium ion such as [mesitylene-H]⁺ and a deuterated aromatic solvent to bring about statistical H/D scrambling by an electrophilic aromatic substitution mechanism (Scheme 1).¹²

Experiments with *p*-terphenyl (**1**) as the first substrate indicated a high activity of [mesitylene-H][B(C₆F₅)₄]⁺ and [mesitylene-H][CHB₁₁H₅Cl₆]⁺ as deuteration catalysts. Using a 10 mol % catalyst loading in C₆D₆, **1-d**₁₄ was formed within hours at room temperature with a high degree of deuterium incorporation (>90% D) as evidenced by GC–MS analysis (Figure 1). Side reactions such as oligomerization were not observed. The two anions gave practically identical results, and because of the significantly lower price of the tetraarylborate, [mesitylene-H][B(C₆F₅)₄]⁺ was chosen for most of the preparative-scale experiments. With 5 mol % of catalyst, performing the reaction for 24 h at room temperature afforded **1-d**₁₄ in 98% isolated yield (Table 1, entry 1). Quantification of

residual hydrogen atoms by ¹H NMR spectroscopy gave a deuteration degree of 96% D. This value was in good agreement with an analysis of the mass spectroscopic isotope pattern, which indicated 94% D incorporation.¹³

Fluoranthene (**2**), pyrene (**3**), and triphenylene (**4**) also underwent clean perdeuteration (Table 1, entries 2–4 and Figure 2). **3-d**₁₀ was formed at a much slower rate than the other products. At room temperature, almost no H/D exchange took place over days. Heating the reaction mixture to 70 °C for 3 days furnished partially labeled **3** in 96% yield (ca. 90% D). Resubjecting this sample to a second deuteration cycle eventually gave **3-d**₁₀ in a 90% overall yield and with 99% D. For all products, determination of the amount of residual hydrogen atoms by ¹H NMR spectroscopy and analysis of their isotope pattern gave comparable % D values.

Characterization of the products by ¹³C NMR spectroscopy showed characteristic triplets for the labeled carbon atoms resulting from the ²H nuclear spin of *S* = 1. Recording the spectra under standard conditions, i.e., with proton decoupling, gave signals with unproportionally intense resonances from minor isotopologs even with a pulse delay of 30 s (**4-d**₁₂, Figure 3a).¹⁴ That the additional signals are not impurities or artifacts could be demonstrated by recording the spectra without ¹H decoupling and with the addition of Cr(acac)₃ (0.005 M) as a paramagnetic relaxation agent. The relaxation time *T*₁ of all carbon atoms is significantly reduced in this case, and near-quantitative integration is achieved with a pulse delay of 1 s. Spectra devoid of the extra signals were obtained, confirming the high degree of deuteration inferred from ¹H NMR and MS data (Figure 3b; see also pp S12/13 in the Supporting Information for ¹³C NMR spectra of **1-d**₁₄).

Kilogram scale synthesis of corannulene (**5**) made feasible the contemplation of a broader range of physical studies such as neutron diffraction and solid state dynamic NMR. Missing was

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Scheme 1. Mesitylenium Ion Catalyzed H/D Exchange at Aromatic C–H Positions via Wheland Intermediates

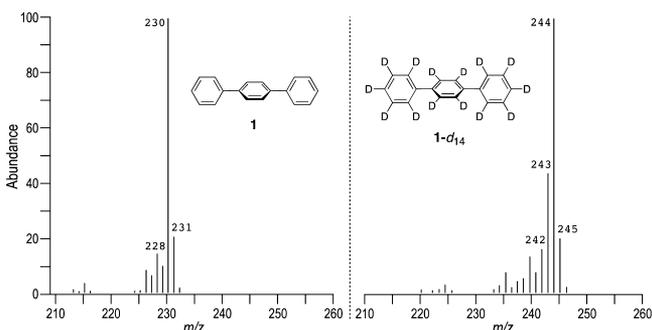
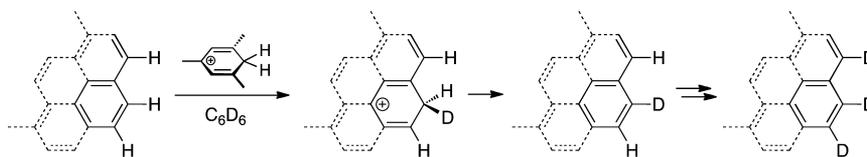


Figure 1. EI-MS analysis of *p*-terphenyl (**1**) before (left) and after (right) deuteration using [Mes–H][B(C₆F₅)₄] in C₆D₆.

a clean preparation of **5-d**₁₀.¹⁵ Due to its extended π system and curved geometry, **5** is more prone to oxidation/reduction and other side reactions than substrates **1–4**. H/D exchange of **5** took place in either C₆D₆ or toluene-*d*₈ at room temperature; however, the reaction occurred more cleanly in toluene-*d*₈. In order to obtain analytically pure product, silica gel chromatography followed by preparative HPLC was necessary and afforded **5-d**₁₀ in 76% yield and with 96% D incorporation.

Mesitylenium acids have been demonstrated to be efficient H/D exchange catalysts for polycyclic aromatic compounds.¹⁶ The reactions can be performed without the need for high temperatures or pressures in relatively inexpensive deuterated aromatic solvents. The excellent yields and degrees of deuterium incorporation are anticipated to allow for the direct

Table 1. Deuteration of Polycyclic Aromatic Substrates (60 mg Scale)

Entry	Starting material	Conditions	Product	Yield	% D ^a
1		[Mes–H][B(C ₆ F ₅) ₄] (4.9 mol%) 0.12 M in C ₆ D ₆ RT, 24 h		98%	96 (94)
2		[Mes–H][B(C ₆ F ₅) ₄] (6.0 mol%) 0.15 M in C ₆ D ₆ RT, 24 h		93%	94 (95)
3		[Mes–H][B(C ₆ F ₅) ₄] (6.7 mol%) 0.14 M in C ₆ D ₆ 70 °C, 3 d		96% 90% ^b	90 (89) 99 (99) ^b
4		[Mes–H][B(C ₆ F ₅) ₄] (6.1 mol%) 0.13 M in C ₆ D ₆ RT, 24 h		98%	94 (95)
5		[Mes–H][CHB ₁₁ H ₅ Cl ₆] (5.2 mol%) 0.13 M in toluene- <i>d</i> ₈ RT, 14 d		76%	96 (96)

^aDetermined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard; numbers in parentheses were determined by analysis of the MS isotope pattern. ^bAfter resubjecting the isolated product to a second deuteration cycle; see the Supporting Information for full experimental details.

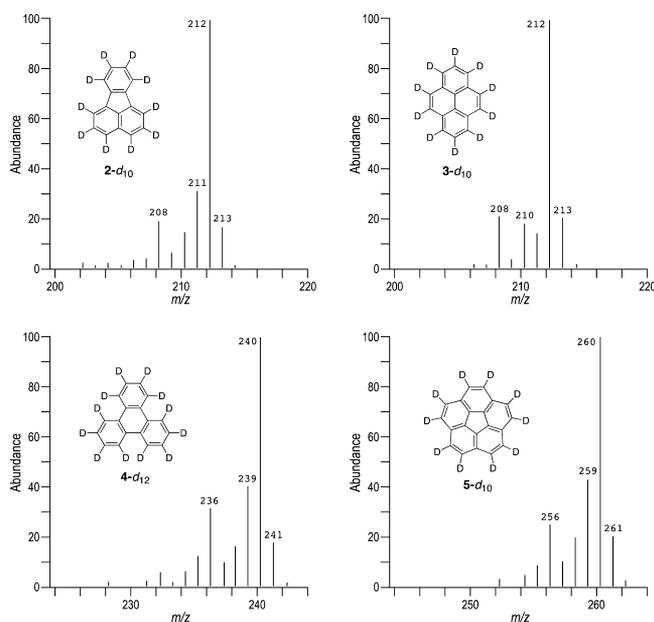


Figure 2. EI-MS analysis of perdeuterated products.

preparation of perdeuterated molecules of interest or of labeled building blocks for further utilization in organic synthesis.

EXPERIMENTAL SECTION

General Information. Reaction Conditions. All glassware was dried at 150 °C for at least 12 h and allowed to cool in a vacuum. Catalyst preparation and deuteration reactions were performed in a glovebox under a nitrogen atmosphere with O₂, H₂O <1 ppm. Solvents for the preparation of catalysts and deuteration reactions were dried by distillation from sodium benzophenone ketyl and stored over 3 Å molecular sieves. Molecular sieves were activated by heating them to 150 °C for several days and allowing them to cool in a vacuum.

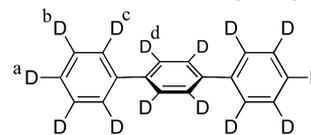
Chemicals. Starting materials 1–4 (*p*-terphenyl, fluoranthene, pyrene, and triphenylene) were of >95% grade and commercially available. Corannulene (5) and mesitylenium acids were synthesized by literature procedures.^{17–20} The mesitylenium acids were generated by adding 2 equiv of triflic acid to the silyl cation intermediates instead of using HCl gas. Deuterated solvents (99% D) were commercially

available. For workup and silica gel purification distilled solvents of technical grade were used; for HPLC purification HPLC grade solvents were used.

Characterization. NMR spectra were recorded on 500 MHz (¹H) instruments. Data are reported as follows: chemical shift in ppm, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constant *J* in Hz, integration, and interpretation. Signals were referenced against solvent peaks (¹H, residual CHDCl₂ = 5.32 ppm; ¹³C, CD₂Cl₂ = 54.0 ppm). For the determination of deuterium incorporation by NMR spectroscopy, 1,3,5-trimethoxybenzene was used as an internal standard, and its aromatic signal was compared to the sum of residual protons of the deuterated products; a delay time *d*1 (time between two pulses) of 30 s was chosen for accurate integration. ¹³C{¹H} NMR spectra were recorded with *d*1 = 30 s.

GC–MS data were obtained using EI ionization (70 eV). High-resolution mass spectra were measured using ESI-TOF spectroscopy.

Synthesis of Deuterated Products. *p*-Terphenyl-*d*₁₄.



Chemical Formula: C₁₈D₁₄
Exact Mass: 244.197
Molecular Weight: 244.390

An 8 mL vial was charged with *p*-terphenyl (54.0 mg, 234 μmol), [mesitylene–H][B(C₆F₅)₄] (9.2 mg, 11.5 μmol, 4.9 mol %), C₆D₆ (2 mL), and a stir bar. The mixture was stirred for 24 h, and the vial was taken out of the glovebox into a fumehood. H₂O (1 mL) and conc aq NH₄Cl (1 mL) were added, and the mixture was extracted with CH₂Cl₂ (3 × 2 mL). The organic layers were filtered through silica gel (2 cm in a Pasteur pipet) and evaporated to dryness. The obtained solid was redissolved in CH₂Cl₂ (2 mL) and again filtered through silica gel (3 cm in a Pasteur pipet, eluent CH₂Cl₂). Concentration of the filtrate and drying in a vacuum at room temperature gave the product as a colorless microcrystalline solid (56.2 mg, 98%). Deuterium incorporation based on ¹H NMR spectroscopy: 96% D. Deuterium incorporation based on MS isotope pattern: 94% D. Mp = 207–209 °C. ¹H NMR (500 MHz, CD₂Cl₂): δ 7.72–7.71 (m, 4 H, H^a), 7.69–7.66 (m, 4 H, H^c), 7.49–7.44 (m, 7 H, H^b)*, 7.39–7.37 (m, 2 H, H^a). *Integration indicates that H/D exchange at this position occurs more slowly than at the other positions. The assignment of this signal is based on the ¹H NMR spectrum of the nondeuterated starting material. ¹³C{¹H} NMR (125 MHz, CD₂Cl₂): δ 140.9 (s), 140.4 (s),

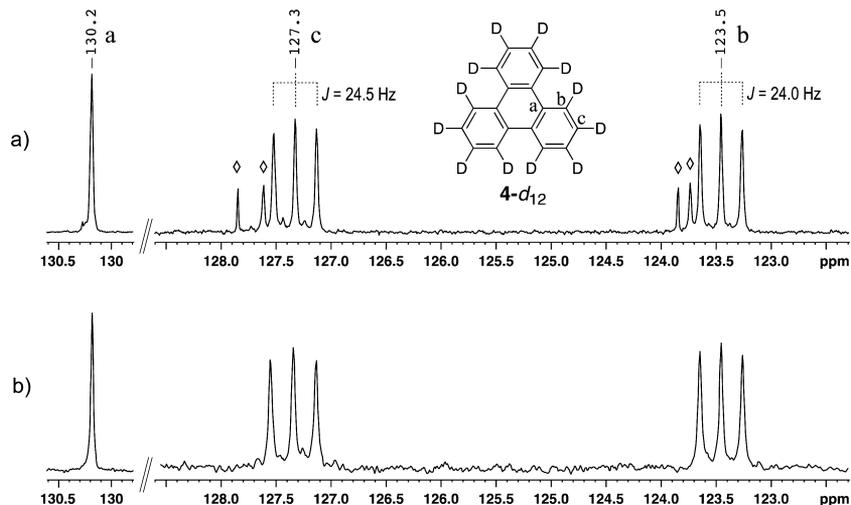
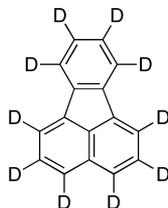


Figure 3. ¹³C NMR spectra of perdeuterated triphenylene (4-*d*₁₂). (a) ¹³C{¹H} spectrum showing major signals from 4-*d*₁₂ and unproportionally intense resonances from 4-*d*₁₁ and 4-*d*₁₀ (marked with diamonds; 125 MHz, 0.19 M in CD₂Cl₂, pulse delay 30 s, 1024 scans). (b) ¹³C NMR spectrum without ¹H decoupling and with 1.0 mg Cr(acac)₃ added as a relaxation agent (125 MHz, 0.10 M in CD₂Cl₂, pulse delay 1 s, 1024 scans).

128.9 (t, $J = 24.3$), 127.5 (t, $J = 24.3$), 127.4 (t, $J = 24.0$), 127.0 (t, $J = 24.1$). MS (EI): 245 (20), 244 (100), 243 (44), 242 (16), 241 (8), 240 (13).

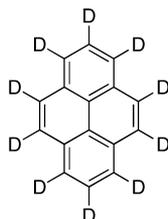
Fluoranthene- d_{10} .



Chemical Formula: $C_{16}D_{10}$
Exact Mass: 212.141
Molecular Weight: 212.312

An 8 mL vial was charged with fluoranthene (59.1 mg, 292 μmol), [mesitylene-H][B(C₆F₅)₄] (14.0 mg, 17.5 μmol , 6.0 mol %), C₆D₆ (2 mL), and a stir bar. The mixture was stirred for 24 h, and the vial was taken out of the glovebox into a fumehood. H₂O (1 mL) and conc aq NH₄Cl (1 mL) were added, and the mixture was extracted with CH₂Cl₂ (3 \times 2 mL). The organic layers were filtered through silica gel (3 cm in a Pasteur pipet) and evaporated to dryness to afford the product as a yellowish microcrystalline solid (57.5 mg, 93%). Deuterium incorporation based on ¹H NMR spectroscopy: 94% D. Deuterium incorporation based on MS isotope pattern: 95% D. Mp = 104–105 °C. ¹H NMR (500 MHz, CD₂Cl₂): δ 8.00–7.97 (m, 2 H), 7.97–7.94 (m, 2 H), 7.90–7.87 (m, 2 H), 7.69–7.65 (m, 2 H), 7.44–7.40 (m, 2 H). ¹³C{¹H} NMR (125 MHz, CD₂Cl₂): δ 139.9 (s), 137.3 (s), 132.9 (s), 130.4 (s), 128.1 (t, $J = 24.3$), 127.6 (t, $J = 24.4$), 126.7 (t, $J = 24.4$), 121.7 (t, $J = 24.5$), 120.3 (t, $J = 24.5$). MS (EI): 213 (17), 212 (100), 211 (31), 210 (15), 209 (6), 208 (19).

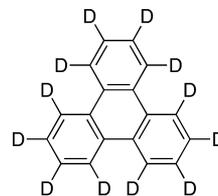
Pyrene- d_{10} .



Chemical Formula: $C_{16}D_{10}$
Exact Mass: 212.141
Molecular Weight: 212.312

An 8 mL vial was charged with pyrene (56.7 mg, 280 μmol), [mesitylene-H][B(C₆F₅)₄] (15.0 mg, 18.7 μmol , 6.7 mol %), C₆D₆ (2 mL), and a stir bar. The vial was taken out of the glovebox into a fumehood and heated to 70 °C for 3 days. H₂O (1 mL) and conc aq NH₄Cl (1 mL) were added, and the mixture was extracted with CH₂Cl₂ (3 \times 2 mL). The organic layers were filtered through silica gel (3 cm in a Pasteur pipet) and evaporated to dryness to afford the product as a yellowish microcrystalline solid (57.1 mg, 96%). ¹H NMR integration vs internal 1,3,5-trimethoxybenzene standard indicated 90% deuterium incorporation; 89% D based on MS isotope pattern. 26.7 mg of this material was resubjected to the deuteration conditions for 1 d at 70 °C (7.1 mol % catalyst loading). Identical workup and silica gel filtration afforded the product as a yellowish microcrystalline solid (25.1 mg, 94%, 90% overall yield). Deuterium incorporation based on ¹H NMR spectroscopy: 99% D. Deuterium incorporation based on MS isotope pattern: 99% D. Mp = 143–144 °C. ¹H NMR (500 MHz, CD₂Cl₂): δ 8.23–8.21 (m, 4 H), 8.12–8.10 (m, 4 H), 8.06–8.02 (m, 2 H). ¹³C{¹H} NMR (125 MHz, CD₂Cl₂): δ 131.6 (s), 127.4 (t, $J = 24.4$), 126.0 (t, $J = 24.3$), 125.1 (s), 125.0 (t, $J = 24.3$). MS (EI): 213 (20), 212 (100), 211 (14), 210 (18), 209 (4), 208 (21).

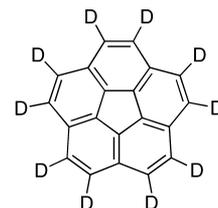
Triphenylene- d_{12} .



Chemical Formula: $C_{18}D_{12}$
Exact Mass: 240.169
Molecular Weight: 240.362

An 8 mL vial was charged with triphenylene (60.4 mg, 265 μmol), [mesitylene-H][B(C₆F₅)₄] (13.0 mg, 16.2 μmol , 6.1 mol %), C₆D₆ (2 mL), and a stir bar. The mixture was stirred for 24 h, and the vial was taken out of the glovebox into a fumehood. H₂O (1 mL) and conc aq NH₄Cl (1 mL) were added, and the mixture was extracted with CH₂Cl₂ (3 \times 2 mL). The organic layers were filtered through silica gel (3 cm in a Pasteur pipet) and evaporated to dryness to afford the product as a colorless powder (62.3 mg, 98%). Deuterium incorporation based on ¹H NMR spectroscopy: 94% D. Deuterium incorporation based on MS isotope pattern: 95% D. Mp = 194–195 °C. ¹H NMR (500 MHz, CD₂Cl₂): δ 8.70–8.66 (m, 6 H), 7.71–7.67 (m, 6 H). ¹³C{¹H} NMR (125 MHz, CD₂Cl₂): δ 130.2 (s), 127.3 (t, $J = 24.5$), 123.5 (t, $J = 24.0$). MS (EI): 241 (18), 240 (100), 239 (40), 238 (17), 237 (10), 236 (32), 235 (13).

Corannulene- d_{10} .



Chemical Formula: $C_{20}D_{10}$
Exact Mass: 260.141
Molecular Weight: 260.355

A 20 mL vial was charged with corannulene (500 mg, 2.00 mmol), [mesitylene-H][CHB₁₁H₃Cl₆] (25.0 mg, 53.0 μmol , 2.7 mol %), toluene-*d*₈ (15 mL), and a stir bar. The mixture was stirred at room temperature. After 6 d, additional [mesitylene-H][CHB₁₁H₃Cl₆] (25.0 mg, 53.0 μmol , 2.7 mol %) was added. After a total stirring time of 2 weeks the reaction was quenched with D₂O (3 mL). The aqueous phase was extracted with EtOAc (3 \times 5 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in a vacuum. Flash column chromatography (silica gel, eluent hexanes) removed baseline impurities; the sample was then further purified by preparative HPLC (Water Spherisorb S5 CN 20 \times 250 mm column, eluent hexane–CH₂Cl₂ 95:5, flow 15.0 mL/min, 50 mg crude product in 20 mL solvent mixture, \sim 4 mL/run, retention time 8.5–9.5 min). The product was obtained as colorless crystals (395 mg, 76%). Deuterium incorporation based on ¹H NMR spectroscopy: 96% D. Deuterium incorporation based on MS isotope pattern: 96% D. Mp = 250–251 °C. ¹H NMR (500 MHz, CD₂Cl₂): δ 8.86–8.63 (m). ¹³C{¹H} NMR (125 MHz, CD₂Cl₂): δ 136.3 (s), 131.4 (s), 127.2 (t, $J = 24.4$). MS (EI): 261 (20), 260 (100), 259 (43), 258 (20), 257 (10), 256 (25), 255 (9). HR-MS (ESI-TOF) exact mass calculated for [C₂₀D₁₀]⁺* 260.1410; found 260.1407.

■ ASSOCIATED CONTENT

📄 Supporting Information

GC–MS data and ¹H/¹³C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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