Fluorination Capabilities of Xenon Fluoride/Graphite Intercalates: Introduction of Fluorine into Carcinogenic Polycyclic Aromatic Hydrocarbons

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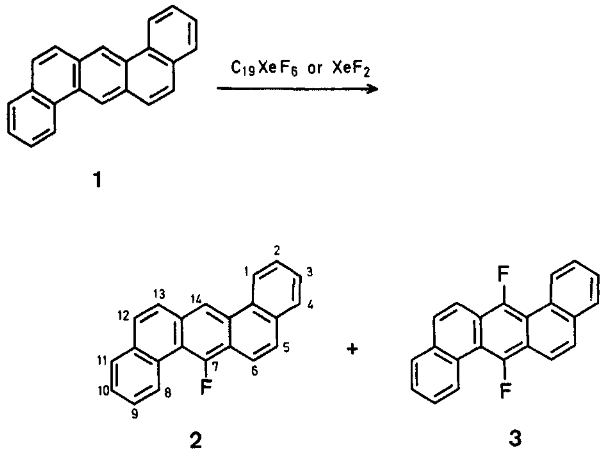
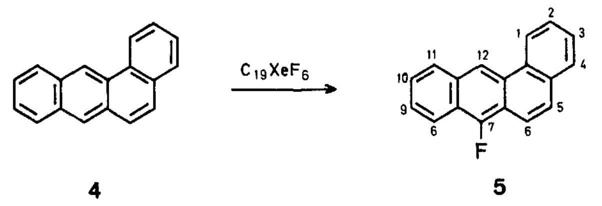
Fluorine substituted polycyclic aromatic hydrocarbons have been prominent in the study of structure-activity relationships of chemical carcinogens in this series[1,2]. Direct methods for the introduction of a fluorine atom into polycyclic aromatic hydrocarbons are still in their infancy[3]. The unsatisfactory "state of the art" in the carcinogenic polycyclic aromatic hydrocarbons has somewhat changed with the synthesis of 6-fluorobenzo[*a*]pyrene by the fluorination of benzo[*a*]pyrene with xenon difluoride[4]. Generally, however, the fluorination capabilities of xenon fluorides are limited, in view of their extreme aggressive properties. The taming of the shrewish xenon hexafluoride has recently been realized with the preparation of its intercalate with graphite[5]. The moderating influence of the graphite makes the intercalate a novel and useful fluorinating agent in aromatic systems. We report the application of the $C_{19}XeF_6$ intercalate as a mild selective fluorination agent of carcinogenic polycyclic aromatic hydrocarbons.

The fluorination of the highly carcinogenic dibenz[*a,h*]anthracene (**1**) by $C_{19}XeF_6$ illustrates the synthetic potential inherent in the method. The reaction was carried out in dichloromethane solution in a polyethylene bottle in an open system, under anhydrous conditions, without hydrogen fluoride initiation. Careful column chromatography of the crude product on silica gel afforded 7-fluorodibenz[*a,h*]anthracene (**2**) in 17% yield. The structure of **2**, including the site of fluorination, was established by the elemental analyses, the molecular ion at $m/e = 296$ in the mass spectrum, and the chemical shift and pattern of the ^{19}F-N.M.R. spectrum[6]: $\delta = 119.3$ ppm singlet. This shift is significantly shielded, as compared with those of 9-fluoroanthracene[4], 7-fluorobenz[*a*]anthracene (**5**), and 6-fluorobenzo[*a*]pyrene[4] [$\delta = 131.8$ ($CDCl_3$), 131.9 ($CDCl_3$), and 132.0 ppm (CH_2Cl_2), respectively][6]. The characteristic two proton singlet at $\delta = 9.01$ ppm in the ^{1}H-N.M.R. spectrum of the parent hydrocarbon **1** (in CS_2), attributed to H-7 and H-14[7], appeared in the corresponding spectrum of **2** as a one proton singlet at $\delta = 8.96$ ppm, ascribed to H-14. The U.V. spectrum of **2** was very similar to that of **1**, 5-fluorodibenz[*a,h*]anthracene[9], and 6-fluorodibenz[*a,h*]anthracene[10]. It should be noted that the synthesis of **2** differs from the previously reported direct synthesis of fluorine-substituted polycyclic aromatic hydrocarbons[3,4,11,12,13] not only in the fluorination reagent but also in the site of aromatic substitution: position 7 in dibenz[*a,h*]anthracene (**1**) is highly hindered as compared with the previously reported sites of substitution, (e.g., position 9 in anthracene[11], position 6 in benzo[*a*]pyrene[4], or position 9 in phenanthrene[11,12,13]). The formation of **2** is in line with the enhanced reactivity of position 7 of **1** towards electrophilic reagents[14].

The synthesis of **2** was accomplished alternatively via the xenon difluoride route[3]. Treatment of **1** with xenon difluoride in dichloromethane solution in an open system, under anhydrous conditions gave a crude mixture of fluorination products, as indicated by the ^{19}F-N.M.R. spectrum[6]: δ ($CDBr_3$, 75°) = 119.3 (s), 123.4 (s) and 125.6 ppm (d, $J \sim 11$ Hz) relative areas 7:3:7, respectively). Careful column chromatography followed by successive recrystallizations afforded pure **2** in 22% yield. However, it was preceded by another fluorination product, probably impure 7,14-difluorodibenz[*a,h*]anthracene (**3**)[15]. This structural assignment is based on the molecular ion at $m/e = 314$ in the mass spectrum and the identity of the ^{19}F-N.M.R. spectrum [δ ($CDBr_3$, 75°) = 123.4 ppm, singlet] with that of an authentic sample of **3** prepared by a "tailor-made" route[16]. The remaining ^{19}F-N.M.R. doublet at $\delta = 125.6$ ppm of the crude reaction mixture may be due to the 6-fluoro derivative. For comparison, the corresponding absorption of the 5-fluoro derivative and 9-fluorophenanthrene are 125.6 ppm (unresolved multiplet, $\nu_{1,2} = 25$ Hz) and 125.2 ppm[13], respectively.





The fluorination capabilities of the graphite/xenon hexafluoride intercalate were further explored in the carcinogenic polycyclic aromatic hydrocarbon series by application to benz[*a*]anthracene (**4**). Column chromatography of the crude reaction mixture on alumina afforded (apart from the starting parent hydrocarbon) 7-fluorobenz[*a*]anthracene (**5**) in 22% yield. The ^{19}F-N.M.R. spectrum ($\delta = 131.9$ ppm singlet)[6] established the site of substitution, indicating a preference of position 7 over the sterically hindered position 12.

This conclusion was substantiated by the ^{1}H-N.M.R. spectrum[6] which contained *(inter alia)* one downfield singlet at $\delta = 8.73$ ppm representing H-12, versus two singlets at 9.07 (H-12) and 8.27 ppm (H-7) in the corresponding spectrum of **4**. The fluorination of **4** with xenon difluoride gave predominantly **5** in 31% yield. In this reaction, however, a possible formation of 12-fluorobenz[*a*]anthracene was suggested by the additional ^{19}F-N.M.R. absorption at 119.0 ppm (singlet)[6] of the crude mixture.

The advantages of the intercalate route stem from the convenience of handling the fluorinating agent: it is practically a shelf reagent. The preparation of **2** by a direct action of $C_{19}XeF_6$ on **1** widens the scope and generality of this fluoroaromatic synthesis. It illustrates the applicability of this straightforward route to the synthesis of fluorine-substituted carcinogenic polycyclic aromatic hydrocarbons. The versatility of the reaction is manifested by the feasibility of directing the reaction to highly hindered sites of substitution. The results seem to indicate that the xenon hexafluoride/graphite intercalate is a more selective fluorinating agent compared with xenon difluoride.

Caution. The reactions were carried out in a well-ventilated hood. Great care was taken to observe the strict precautions[17] for handling carcinogenic polycyclic aromatic hydrocarbons, including the use of dispensible gloves and masks.

7-Fluorodibenz[*a,h*]anthracene (2):

Method A: Fluorination with $C_{19}XeF_6$: A solution of **1** (1.00 g, 3.6 mmol; Fluka AG, Buchs, Switzerland) in dry dichloromethane (150 ml) was added at −196° under anhydrous conditions to $C_{19}XeF_6$[5] (1.80 g, 3.8 mmol) in a polyethylene bottle. The magnetically stirred reaction mixture was gradually warmed to room temperature and stirred for 30 h. The graphite was filtered off from the dark blue mixture and washed with dichloromethane. The organic fractions were washed successively with aqueous sodium hydrogen carbonate (twice) and water, dried with sodium sulfate, and the solvent evaporated to dryness under vacuum. The crude product was purified by column chromatography on silica gel, using a mixture of petroleum ether (b.p. 40–60°) and dichloromethane (20:1) as an eluent. Compound **2** was obtained as light yellow needles; yield: 170 mg (16%); m.p. 202–203° (from butanol).

T.L.C. [silica, petroleum ether (b.p. 40–60°)/dichloromethane (20:1)], R_f (**2**) = 0.51; R_f (**1**) = 0.40.

$C_{22}H_{13}F$	calc.	C 89.20	H 4.39	F 6.42
(296.3)	found	89.45	4.62	6.29

^{19}F-N.M.R. ($CDBr_3$, 75°):[6] $\delta = 119.3$ ppm (s).

^{1}H-N.M.R. ($CDBr_3$, 90°):[6] $\delta = 8.96$ (s, 1H, H-14), 8.90–8.54 (m, 2H, H-1, H-8), 8.20–7.46 ppm (m, 10H, H-2, H-3, H-4, H-5, H-6, H-9, H-10, H-11, H-12, H-13).

U.V. (cyclohexane): $\lambda_{max} = 222$ ($\varepsilon = 49000$), 230s (21000), 277 (49000), 288 (99000), 297 (140000), 322 (16000), 335 (14200), 348 (10800), 375 (1280), 396 nm (1100).

I.R. (KBr): $\nu_{max} = 1440$, 1315, 1240, 1060, 940, 885, 800, 740, 655, 525 cm^{-1}.

Method B: Fluorination with XeF_2: A solution of **1** (1.4 g, 5.0 mmol) in dry dichloromethane (170 ml) was added at −196° under anhydrous conditions and with magnetic stirring to xenon difluoride (0.9 g, 5.3 mmol) in a polyethylene bottle. The reaction mixture was gradually warmed to room temperature and stirred for 30 h. After 6 h, a change of color from yellow to dark blue was observed. Xenon evolution was also observed during the reaction. The reaction mixture was decomposed with aqueous sodium hydrogen carbonate. The organic layer was washed with water and dried with sodium sulfate and the solvent removed under vacuum. The remaining crude mixture was purified by column chromatography on silica gel, using a mixture of petroleum ether (b.p. 40–60°) and dichloromethane (20:1) as an eluent. Compound **3** was first eluted from the column and was obtained as light yellow needles; m.p. 204° (from butanol); Lit.[16], m.p. 213–215°.

T.L.C. (silica, petroleum ether (b.p. 40–60°)/dichloromethane (20:1), R_f (**3**) = 0.58.

^{19}F-N.M.R.: $\delta = 123.4$ ppm (s).

Compound **3** was followed by **2** which was obtained as light yellow needles; yield: 330 mg (22%); m.p. 202–203° (from 1-butanol); mixture m.p. with a sample prepared by method A, 202°.

$C_{22}H_{13}F$	calc.	C 89.20	H 4.39	F 6.42
(296.3)	found	89.00	4.49	6.42

7-Fluorobenz[a]anthracene (5):

Benz[*a*]anthracene (400 mg, 1.75 mmol; Fluka AG) was fluorinated with $C_{19}XeF_6$ (800 mg, 1.8 mmol) analogously to **1**. The ^{19}F-N.M.R. spectrum of the crude product contained a prominent absorption at 131.9 ppm and a very small absorption at 80 ppm (impurity). Column chromatography of the crude product on alumina, using petroleum ether (b.p. 40–60°) as eluent afforded **5** as pale yellow crystals; yield: 95 mg (22%); m.p. 77° (from ethanol); Lit.[18], m.p. 61°.

T.L.C. [alumina, petroleum ether (b.p. 40–60°)]: R_f (**5**) = 0.54; R_f (benz[*a*]anthracene) = 0.41.

$C_{18}H_{11}F$	calc.	C 87.80	H 4.47	F 7.72
(246.3)	found	87.94	4.43	7.38

^{19}F-N.M.R. ($CDCl_3$, 30°):[6] $\delta = 131.9$ ppm (singlet).

U.V. (cyclohexane): $\lambda_{max} = 220$ ($\varepsilon = 35000$), 230 (32000), 251 (31000), 256 (34000), 269 (42000), 279 (85000), 290 (107000), 318 (45000), 333 (7000), 349 (8000), 362 (5200), 367 (5600), 378 (1200), 386 nm (1100).

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