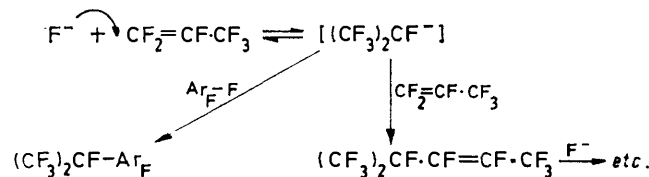


Reactions involving Fluoride Ion. Part IV.^{1,2} Synthesis and Rearrangement of Perfluoroisopropylpyridines

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Synthesis of perfluoropolyisopropylpyridines by fluoride-ion-initiated reactions of hexafluoropropene with pentafluoropyridine at atmospheric pressure is described. Trisubstitution gives a mixture of perfluoro-2,4,5- and 2,4,6-tri-isopropylpyridines; the ratio of these varies with reaction temperature but the 2,4,5-isomer can be obtained as the principal product. The 2,4,5-isomer is rearranged to the 2,4,6-isomer, together with other products, by heating with caesium or potassium fluoride. Cross-over experiments with heptafluoroquinoline have shown that the mechanism of this rearrangement is entirely intermolecular. The mechanism of the polyfluoroalkylation process is discussed.

IN this series we are developing an analogy between the role of fluoride ion in initiating polyfluoroalkylation reactions between fluoro-olefins and activated fluoroaromatic compounds, and the role of a proton in initiating Friedel-Crafts alkylation of aromatic compounds by olefins. The analogy is now further extended to include a fluoride-ion-induced rearrangement of a polyfluoroalkylaromatic system.² We have already described the formation of perfluoroisopropyl derivatives of pyridine³ and pyridazine¹ from hexafluoropropene, but the olefin (I) is, itself, susceptible to



nucleophilic attack and so self-condensation³⁻⁵ to give dimers and trimers competes with the polyfluoroalkylation process.

In an earlier paper,³ the results were reported of reactions between hexafluoropropene (I) and pentafluoropyridine (II), carried out using autoclaves under

¹ Part III, R. D. Chambers, Yu. A. Cheburkov, J. A. H. MacBride, and W. K. R. Musgrave, *J. Chem. Soc. (C)*, 1971, 532.

² Preliminary communication, R. D. Chambers, R. P. Corbally, J. A. Jackson, and W. K. R. Musgrave, *Chem. Comm.*, 1969, 127.

pressure; under these conditions it was difficult to produce reasonable amounts of trisubstituted compounds [*i.e.* (V) and (VI)] in competition with the self-condensation reaction. Since that time, however, we have discovered that the reactions may be carried out more conveniently using atmospheric pressure conditions, which reduces the concentration of olefin in solution and allows polyfluoroalkylation to compete more effectively. Fluorine-19 n.m.r. studies reported elsewhere⁶ established that a mixture of isomeric perfluoro-2,4,5- (V) and 2,4,6- (VI) tri-isopropylpyridines is obtained. These isomers are difficult to separate; on the stationary phases available to us only partial resolution occurred on analytical scale g.l.c., and preparative-scale isolation of (V) and (VI), individually, was not feasible.

Therefore, experiments were carried out, initially, to determine the optimum conditions for the preparation of the 2,4,5-isomer (V); the results are shown in Table I. These experiments involved use of a flow system in which the olefin, alone or diluted with nitrogen, was recirculated through the reaction mixture, which was vigorously stirred. Starting with a 3:1 molar or

³ R. D. Chambers, J. A. Jackson, W. K. R. Musgrave, and R. A. Storey, *J. Chem. Soc. (C)*, 1968, 2221.

⁴ W. J. Brehm, K. G. Bremer, H. S. Eleuterio, and R. W. Meschke, U.S.P. 2,918,501/1959.

⁵ W. Brunskill, W. T. Flowers, R. Gregory, and R. N. Haszeldine, *Chem. Comm.*, 1970, 1444.

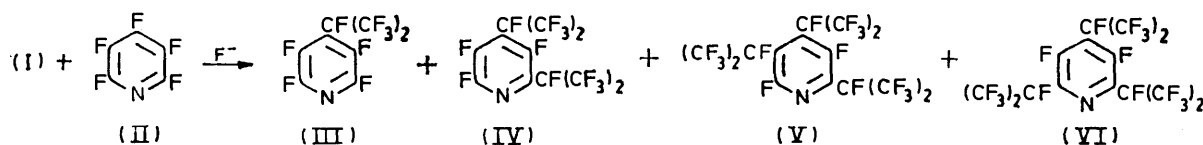
⁶ R. D. Chambers, J. A. Jackson, W. K. R. Musgrave, L. H. Sutcliffe, and G. J. T. Tiddy, *Tetrahedron* 1970, **26**, 71.

TABLE 1

Fluoride-ion induced reactions of hexafluoropropene with pentafluoropyridine							
Experiment:	1	2	3	4	5	6 ^b	7
Reagent ^a (g)							
C ₅ F ₅ N	6.2	5.5	5.6	6.5	6.2	4.7	6.2
C ₃ F ₆	37	33	28	24	18	14	50
KF	20.2	20.5	20.0	20.4	21.0	21.0	20.4
Conditions							
Time (h)	3.0	2.0	1.5	1.0	0.75	1.5	3.0
Temp. (°C)	78	90	118	136	102	102	102
Yields (% based on C ₅ F ₅ N) ^c							
Recovered C ₅ F ₅ N	Trace	Trace	Trace	Trace	Trace	3	Trace
Perfluoro-4-isopropylpyridine (III)	38	42	23	19	53	24	9
Perfluorodi-isopropylpyridine (IV)	4	5	2	3	8 ^d	3 ^d	1
Perfluorotri-isopropylpyridine [(V) + (VI)]	35	37	50	32	19	36	79
% (V) in [(V) + (VI)] ^e	86.0	85.1	81.7	80.1	83.4	83.7	83.5

^a Tetrahydrothiophen dioxide (150 ml) used as solvent in each case. ^b Olefin diluted with N₂. ^c Material balance is partly made up by dimers and trimers of hexafluoropropene. ^d Shown by ¹⁹F n.m.r. to contain none of the 2,5-isomer (VII). ^e Analysed by ¹⁹F n.m.r. spectroscopy.

greater ratio of hexafluoropropene to pentafluoropyridine, 19–79% of the theoretical yield of a mixture of trisubstituted derivatives (V) and (VI) can be obtained along with (III) and small amounts of (IV). This



mixture was shown by n.m.r. analysis to contain none of the corresponding 2,5-isomer (VII).

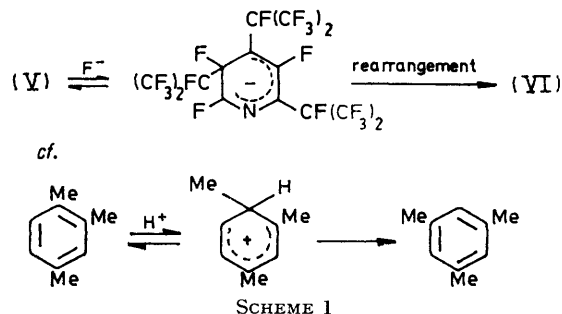
The ratio of isomers (V) and (VI) is variable; results over the range 78–136° indicate that the ratio falls linearly with increase in reaction temperature. A plot of $\ln [(V)/(VI)]$ (molar ratio) against $1/T$ also gave a straight line and from this the difference in activation energies for direct formation of (V) and (VI) was calculated to be 2.3 kcal mol⁻¹. Within experimental error, the ratio (V):(VI) is independent of reaction time at 102° but at 130°, in a separate experiment, approximately 0.5% per hour of (V) was isomerised to (VI), loss of the 4-CF(CF₃)₂ group to give (VII) occurring in preference to migration of the 5-CF(CF₃)₂ group to give (VI) (see later).

Compound (V) was isolated from a mixture of (III), (IV), (V), and (VI); distillation gave a fraction containing only (V) and (VI), from which crystallisation of (V) occurred.

Our interest in this system intensified when we showed that isomer (V) can rearrange to (VI) on heating with fluoride;² this fact suggests the possibility that the

analogy between fluoride-ion- and proton-induced reactions, discussed previously,³ may be extended to include aromatic rearrangements (Scheme 1). It is well known that proton-induced rearrangement of alkylbenzenes can occur by an inter- or an intra-molecular process, depending on the system,⁷ and we have now established that this fluoride-ion-induced rearrangement proceeds by an intermolecular mechanism. This has been achieved by cross-over experiments with perfluoroquinoline which, we have already established,⁸ is reactive towards the polyfluoroalkylation process. Perfluoro-2,4,5-tri-isopropylpyridine (V) is converted completely at 160° during 14 h, in the presence of caesium fluoride, into a mixture of perfluoro-2,4,6-tri-isopropylpyridine (VI) (ca. 50% yield), perfluorodi-isopropylpyridines (IV) and (VII) (2% yield), perfluoro-tetraisopropylpyridine (<1% yield), and traces of condensation products of hexafluoropropene. Under the same conditions, but in the presence of perfluoroquinoline, a perfluoroisopropyl group was almost completely removed from (V). The important point is that the product contained only a small amount of perfluoro-2,4,6-tri-isopropylpyridine (VI) (ca. 4% yield) with no unchanged (V); the mixture also contained perfluoro-2,5-di-isopropylpyridine (VII) (66% yield), perfluoro-2,4-di-isopropylpyridine (IV) (ca. 4% yield), and perfluoroisopropylquinolines, and the latter have been obtained by direct perfluoroalkylation of perfluoroquinoline.⁸ In separate experiments, it was

established that compounds (IV), (VI), and (VII) do not lose perfluoroisopropyl groups under comparable conditions in the presence of perfluoroquinoline; this confirms that the perfluoroisopropyl group is transferred

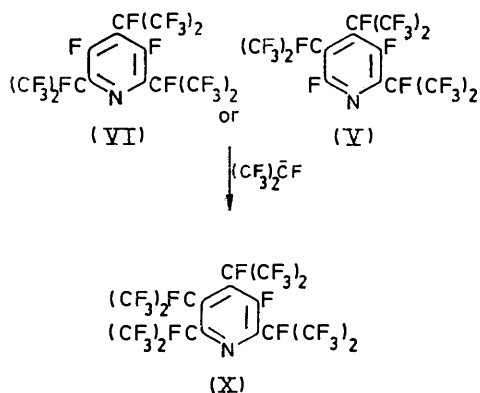


directly from (V). On average, only 56% of quinoline products were recovered (see Table 3); this is due to the instability of the perfluoroquinoline system under the conditions for rearrangement of (V), giving tar. It is notable that the disubstituted pyridines recovered from the cross-over experiments contain much more of

⁸ R. D. Chambers, R. P. Corbally, W. K. R. Musgrave, and (in part) J. A. Jackson and R. S. Matthews, following paper.

⁷ See, e.g., L. M. Stock, 'Aromatic Substitution Reactions,' Prentice-Hall, Englewood Cliffs, New Jersey, 1968, p. 114.

at 190°, with potassium fluoride as catalyst, and small amounts of the same compound were obtained by heating (V) with caesium fluoride at 160°. The structure

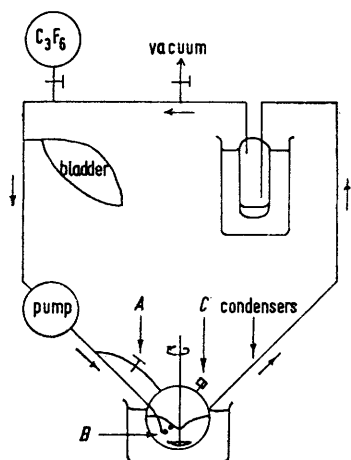


is most likely to be (X) but this could not be confirmed from the ^{19}F n.m.r. spectrum as no ring fluorine signal could be detected; the 3-F signal would be expected to be broad and weak.

EXPERIMENTAL

^{19}F N.m.r. data confirming the structures of compounds described here have been presented in detail elsewhere.⁶

General Technique for Polyperfluoroalkylation of Pentafluoropyridine in a Flow System at Near Atmospheric Pressure.—The apparatus (Figure) consisted of a 250 ml



A flow-system for polyperfluoroalkylation: A, by-pass tap; B, glass sinter; C, serum cap

flask, fitted with a gas-tight stirrer, with one arm connected to reflux condensers leading to a trap cooled in ice-water. An outlet from the trap passed to a small electric pump which circulated gases in the system *via* a second arm of the reaction flask through a sintered glass disc B immersed in the solvent. A by-pass tap A was provided for the sinter, to prevent suck-back, and connections were available for attachment to a vacuum-line and also to a reservoir for the olefin. A football bladder was convenient for this purpose and ensured a constant near-atmospheric pressure in the circuit. The flask was immersed in a thermostatted oil-bath.

In a typical experiment the flask, containing potassium

fluoride (20 g) and tetrahydrothiophen dioxide (150 ml), was evacuated to 10^{-2} mmHg and the system was charged with hexafluoropropene until the bladder was inflated. Pentafluoropyridine (6 g) was injected into the flask through a serum cap C and the mixture was stirred vigorously with the circulating pump in operation. In an experiment at 102° the stirring was continued for 45 min, after which volatile material was transferred from the flask, under high vacuum, to a trap immersed in liquid air. Product mixtures were analysed by g.l.c. (gas density balance detector) and ^{19}F n.m.r. spectroscopy; the results for various experiments are shown in Table 1. The products from several of these reactions (140 g), *i.e.* containing more than 80% of (V) in (V) and (VI), were combined and distilled (spinning-band column), and a fraction of b.p. 179.5–181° at 761 mmHg (69 g), consisting of a mixture of perfluorotri-isopropylpyridines (V) (85%) and (VI) (15%), when seeded and set aside overnight, deposited crystals. After decanting, the product was further purified by melting, followed by fractional freezing and decanting twice more at room temperature to give large crystals, m.p. 31–31.5°, b.p. 182° at 763 mmHg (Siwoloboff), of *perfluoro-2,4,5-tri-isopropylpyridine* (V) (31 g, 20% based on pyridine) (Found: C, 27.5; F, 70.3; N, 2.3%; *M*, 619. $\text{C}_{14}\text{F}_{23}\text{N}$ requires C, 27.15; F, 70.6; N, 2.25%; *M*, 619), λ_{max} (cyclohexane) 211 and 285 nm ($\log \epsilon$ 3.73 and 4.02), λ_{max} (film) 6.25w, 6.4w, 7.0s, 7.4w, 7.75–8.1s, 8.48, 8.6, 8.8w, 9.17, 9.58, 9.88s, 10.16, 10.34s, 11.15w, 12.2s, 12.75w, 12.87w, 13.3s, 13.47s, 13.82, 14.03w, 14.3, 14.9, 15.8w, 16.65w, 17.7w, 18.15, 18.43, and 19.2 μm .

Perfluorotetraisopropylpyridine (X).—A mixture of perfluoroisopropylpyridines (*ca.* 50 g) containing a large proportion of (VI) was heated with an excess of hexafluoropropene at 190° in the manner already described. A small amount of *perfluorotetraisopropylpyridine* (0.6 g), m.p. 111.5°, slowly crystallised from the product at room temperature (Found: C, 26.35; F, 71.2; N, 2.15%; *M*, 769. $\text{C}_{17}\text{F}_{29}\text{N}$ requires C, 26.55; F, 71.65; N, 1.8%; *M*, 769), λ_{max} (solid) 6.25w, 6.58w, 7.13w, 7.48, 7.75–8.15s, 8.42w, 8.54s, 8.82, 9.18w, 9.3w, 10.10s, 10.20s, 10.75, 11.45s, 12.5w, 13.1w, 13.3s, 13.5s, 13.76, 13.95w, 14.25, 15.38w, 15.8w, 18.35w, and 18.6w μm .

Isolation of Perfluoro-2,4-di-isopropylpyridine (IV).—Perfluoro-2,4-di-isopropylpyridine (IV) was isolated, from the products of polyperfluoroalkylation of pentafluoropyridine at 102° shown in Table 1, by preparative-scale g.l.c. on a column of di-*n*-decyl phthalate at 110°, and was obtained as an oil, b.p. 158° at 763 mmHg (Siwoloboff) (Found: C, 28.2; F, 68.6; N, 3.3%; *M*, 469. Calc. for $\text{C}_{11}\text{F}_{17}\text{N}$: C, 28.15; F, 68.85; N, 3.0%; *M*, 469), λ_{max} (cyclohexane) 208 and 274 nm ($\log \epsilon$ 3.40 and 3.70), λ_{max} 6.15w, 6.23w, 6.73s, 6.88, 7.6–8.1s, 8.4–8.5s, 8.7, 8.86, 9.3, 9.45w, 9.92w, 10.0w, 10.17s, 11.33, 11.58, 11.8w, 12.85w, 12.93w, 13.3, 13.5, 13.75, 13.83s, 14.08w, 14.88, 15.35, 15.55, 16.25w, 16.8w, 18.0w, and 18.6 μm . The liquid was shown, by ^{19}F n.m.r. analysis, to contain none of the 2,5-isomer (VII).

Rearrangement of Perfluoro-2,4,5-tri-isopropylpyridine (V) to *Perfluoro-2,4,6-tri-isopropylpyridine* (VI).—The results of two experiments are shown in Table 2. In each case the mixture of (V), caesium fluoride, and tetrahydrothiophen dioxide, contained in a stainless steel tube (100 ml capacity), was heated, with rotational agitation, in an oil-bath at 160° for 14 h. The product was transferred to a 100 ml flask and volatile material was distilled, at 90°

and 10^{-3} mmHg, into a trap immersed in liquid air. Then the condensate was analysed by ^{19}F n.m.r. spectroscopy and (quantitatively) g.l.c. The residue in the flask was poured into water and extracted with ether and the ether layer was dried (Na_2SO_4) and analysed by g.l.c.

TABLE 2

Rearrangement of perfluoro-2,4,5-tri-isopropylpyridine (V) at 160° during 14 h

Reagents ^a		
(V) ^b (g)	6.1	6.2
CsF (g)	6.3	6.3
Yields of products (%)		
$(\text{C}_3\text{F}_8)_n$ ($n = 1-3$)	Trace	Trace
(VI) ^c	47	53
Perfluorodi-isopropylpyridines (IV) and (VII)	2	3
Perfluoro-4-isopropylpyridine (III)	Trace	Trace
Perfluorotetra-isopropylpyridine (X) ^d	ca. 1	ca. 1
Total % recovery of perfluoropyridines	50	56

^a Tetrahydrothiophen dioxide (40 ml) used. ^b M.p. $30-31^\circ$. ^c Contains no trace of (V). ^d Identified by mixed m.p. with an authentic sample.

Isolation of Pure Perfluoro-2,4,6-tri-isopropylpyridine (VI).—A sample (44 g) of (VI) containing ca. 10% of (V) was heated in a stirred mixture with caesium fluoride (20 g) in tetrahydrothiophen dioxide (150 ml) for 15 h at 180° . The volatile products were fractionated at atmospheric pressure through a spinning-band column. A fraction of b.p. $176-178^\circ$ at 758 mmHg was obtained which slowly deposited crystals of perfluoro-2,4,6-tri-isopropylpyridine (VI), m.p. $25-25.5^\circ$, b.p. 176° at 763 mmHg (Siwoloboff) (Found: C, 26.9; F, 70.5; N, 2.5%; M , 619. $\text{C}_{14}\text{F}_{23}\text{N}$ requires C, 27.15; F, 70.6; N, 2.25%; M , 619), λ_{max} (cyclohexane) 208 and 273 nm ($\log \epsilon$ 3.56 and 3.85), λ_{max} (film) 6.3w, 6.88, 7.6—8.1s, 8.5s, 8.75, 8.93w, 9.3s, 9.95, 10.2s, 10.6s, 12.63w, 12.8w, 12.98w, 13.23w, 13.58, 13.72w, 13.9, 14.6, 15.15w, 15.7, 16.05w, 16.7w, 18.0w, 18.55, and 18.80 μm . ^{19}F N.m.r. analysis confirmed the sample to be free of the 2,4,5-isomer (V).

Cross-over Experiments between Perfluoro-2,4,5-tri-isopropylpyridine (V) and Perfluoroquinoline.—Results of a series of experiments are shown in Table 3. The reactions were carried out under the same conditions as those described for the rearrangement (V) \rightarrow (VI) (Table 2) except for the addition of perfluoroquinoline. The substituted quinoline products were separated by column chromatography on a column of Mallinkrodt Silicar CC7 (100—200 mesh) with light petroleum (b.p. $60-80^\circ$) as eluant followed by preparative g.l.c. on a column of polyethylene glycol *o*-phthalate (20% on AW-Celite 80—100) at 150° . The products were identified by comparison of g.l.c. retention times and i.r., ^{19}F n.m.r., and mass spectra with those of samples prepared independently.⁸

Isolation of Perfluoro-2,5-di-isopropylpyridine (VII).—Compound (VII) was isolated from the products of the cross-over experiments of Table 3 by double preparative-scale g.l.c. on a column of di-*n*-decyl phthalate at 110° , after which it was free of the 2,4-isomer (IV), and was obtained

as an oil, b.p. 159° at 761 mmHg (Siwoloboff) (Found: C, 28.5; F, 69.0; N, 3.35%; M , 469. $\text{C}_{11}\text{F}_{17}\text{N}$ requires C, 28.15; F, 68.85; N, 3.0%; M , 469), λ_{max} (cyclohexane) 214 and 266 nm ($\log \epsilon$ 3.27 and 3.60). The ^{19}F n.m.r. spectrum (neat liquid at 40° ; p.p.m. upfield of external CFCl_3) showed peaks at 56.31 (overlapping heptets, J ca 13 and 25 Hz, 6-F), 76.86 [dd, J 5 and 6 Hz, 2-CF(CF_3)₂], 77.61 [ddd, J 5.5, 11.5, and 14 Hz, 5-CF(CF_3)₂], 108.6 (overlapping heptets, J ca. 12 Hz, 4-F), 144.7br (3-F), 180.7 [d hept + hept, restricted rotation, J 5.5 and 84 Hz, 5-CF(CF_3)₂], and 186.5 [d hept, J 51 and 6 Hz, 2-CF(CF_3)₂],

TABLE 3

Cross-over experiments with perfluoro-2,4,5-tri-isopropylpyridine (V) and perfluoroquinoline (160° ; 14 h)

Reagents ^a			
(V) ^b (g)	6.2	6.2	5.9
Perfluoroquinoline (g)	2.0	2.0	2.0
CsF (g)	6.0	6.0	5.7
Yields of products (%)			
$(\text{C}_3\text{F}_8)_n$ ($n = 1-3$)	Trace	Trace	Trace
(VI) ^c	3	4	4
Perfluorodi-isopropylpyridines	67	76	69
Approx. ratio of (VII) to (IV)	16 : 1	16 : 1	16 : 1
Perfluoro-4-isopropylpyridine (III)	0	Trace	0
Perfluorotri-isopropylquinoline	Trace	Trace	Trace
Perfluoro-2,4-di-isopropylquinoline	8	7	11
Perfluoro-2,6-di-isopropylquinoline	12	10	8
Perfluoroisopropylquinolines	21	25	20
Perfluoroquinoline	8	15	23
Total % recovery of perfluoropyridines	70	80	73
Total % recovery of perfluoroquinolines	49	57	62

^a Tetrahydrothiophen dioxide (40 ml) used. ^b M.p. $30-31^\circ$. ^c Contains no trace of (V).

ν_{max} (film) 6.1w, 6.25w, 6.7, 6.9, 7.13w, 7.6—8.1s, 8.45, 8.68, 8.93w, 9.15w, 9.25, 9.45w, 9.7, 10.0, 10.15—10.25s, 11.35w, 11.45w, 11.55w, 11.67w, 12.35, 12.85w, 13.25, 13.35, 13.48, 13.63w, 13.85w, 14.8w, 15.75w, and 18.54 μm .

Stability of Other Perfluoroisopropylpyridines in Reaction with Caesium Fluoride.—*Isomer (VI).* In separate experiments, the tri-substituted pyridine (VI) (6.4 g) was heated with a mixture of perfluoroquinoline (2.0 g), caesium fluoride (6.2 g), and tetrahydrothiophen dioxide (40 ml) at 160° for 14 h. Only traces of perfluoroisopropylquinolines were detected by g.l.c. and 88% of (VI) was recovered together with 74% of unchanged perfluoroquinoline.

Di-isopropylpyridines (IV) and (VII). In a similar experiment, an approximately 50 : 50 mixture of (IV) and (VII) (5.3 g) was heated with a mixture of caesium fluoride (6.0 g), perfluoroquinoline (2.0 g), and tetrahydrothiophen dioxide (40 ml) at 160° for 14 h. Only a slight trace of a perfluoroisopropylquinoline was detected by g.l.c. and 77% of (IV) and (VII) was recovered, the ratio of isomers being unchanged, together with 89% of unchanged perfluoroquinoline.

We thank the University of Durham for financial support.