Stereochemistry of Bromofluorination of Phenyl-substituted Olefins

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Bromofluorination of phenyl-substituted olefins, *e.g.* 1,1-diphenylethylenes, β-alkylstyrenes, and stilbene, with *N*-bromosuccinimide–hydrogen fluoride–pyridine in ether proceeds with Markovnikov-type regioselectivity. The reaction is sterospecific (*anti*) for *trans*- and nonstereospecific for *cis*-olefins.

AVAILABLE data on the stereochemistry of addition of 'BrF' species to olefins are sparse. In the steroid series [1-3] stereospecific *anti*-addition with anti-Markovnikov-type regioselectivity is observed; on the other hand, the bromofluorination of carbohydrates [4,5] is stereospecifically *syn*. Using hydrogen fluoride–pyridine in conjunction with *N*-bromosuccinimide (NBS) for fluorination of aliphatic olefins, Olah and his co-workers [6] observed typical Markovnikov-type regioselectivity. These differences in reaction pathways prompted us to investigate the fluorination of some phenyl-substituted olefins, *e.g.* 1,1-diphenylethylenes and substituted styrenes, and to study the stereochemistry of bromofluorination of phenyl-substituted olefins, *e.g.* *cis*- and *trans*-1-phenylpropene; *cis*- and *trans*-β-t-butylstyrene and *cis*- and *trans*-stilbene with hydrogen fluoride–pyridine–NBS at 15 °C. We chose these olefins because the stereochemistry of their bromination is well known,[7] and so there was a possibility of drawing conclusions from the stereochemical results about the reaction pathway.

RESULTS AND DISCUSSION

Substituted 1,1-Diphenylethylenes and Styrenes.—The preparation of fluoroalkanes presents a different problem from that of other halogenoalkanes, and necessitates a specific method of fluorination.[8] Difficulties involve the handling of anhydrous hydrogen fluoride on the laboratory scale, the need for pressure equipment and a low temperature, and the ease of polymerisation of alkenes. Bromofluorination with hydrogen fluoride–pyridine–NBS avoids some experimental difficulties,[5] *e.g.* low temperature, high pressure techniques, and polymerisation of olefins. From bromofluorination of the substituted 1,1-diphenylethylenes (1a—e) (Scheme 1) 2-bromo-1-fluoro-1,1-diphenyl products were isolated. All these olefins needed the same reaction time (1 h). The less stable styrene derivatives (1f—h) were also converted in good yield into bromo-fluorides (2f—h). All these reactions were complete after 1 h, except for that of (2h), which needed 3 h. The structures of the products (2a—h) were determined by their i.r., ^{1}H and ^{19}F n.m.r., and mass spectra. In the mass spectra the

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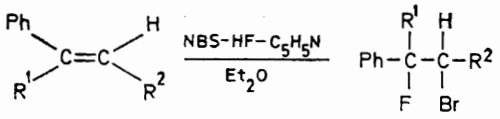
[2] A. Bowers, L. C. Ibanez, E. Denot, and R. Becerra, *J. Amer. Chem. Soc.*, 1960, **82**, 4001.
[3] A. Bowers, E. Denot, and R. Becerra, *J. Amer. Chem. Soc.*, 1960, **82**, 4007.
[4] P. W. Kent and M. R. Freeman, *J. Chem. Soc.* (*C*), 1966, 910.
[5] K. R. Wood, P. W. Kent, and D. Fisher, *J. Chem. Soc.* (*C*), 1966, 912.
[6] G. A. Olah, M. Nojima, and I. Kerekes, *Synthesis*, 1973, 780.
[7] R. C. Fahey, *Topics Stereochem.*, 1968, **3**, 280.
[8] For a review, see W. A. Sheppard and C. M. Sherts, 'Organic Fluorine Chemistry,' Benjamin, New York, 1969.

fragment $[PhCFR^1]^{+\cdot}$ is always the base peak [*m/e* 185 from (2a—e), 109 from (2f and h), and 123 from (2g)]. The addition of fluorine as anion to carbocations was



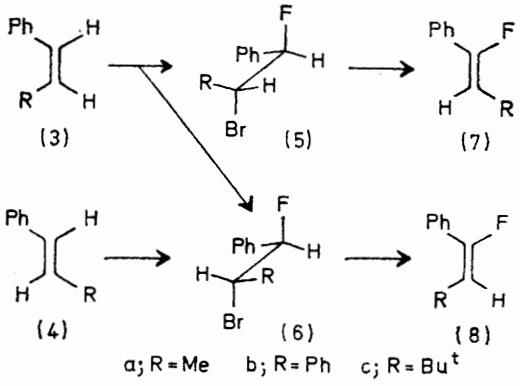
(1) (2)

a; R^1 = Ph, R^2 = H e; R^1 = Ph, R^2 = Br
b; R^1 = Ph, R^2 = Me f; R^1 = R^2 = H
c; R^1 = Ph, R^2 = F g; R^1 = Me, R^2 = H
d; R^1 = Ph, R^2 = Cl h; R^1 = H, R^2 = Br

SCHEME 1

found to occur in accord with Markovnikov-type regioselectivity, forming the corresponding 2-bromo-1-fluoro-1-phenylethanes (2a—h). From the n.m.r. spectra of the crude reaction mixtures we found no evidence for the presence of other products, *e.g.* difluorides, 1-bromo-2-fluoro-1-phenylethanes, or elimination products. Variation of the electronegativity of the substituent on the olefinic carbon atom (H, CH_3, F, Cl, or Br) had no significant influence on the rate of bromofluorination.

Stereochemistry of Bromofluorination of the Phenyl-substituted Olefins (3) *and* (4).—First we consider the identification of the products of the bromofluorination of *cis*- and *trans*-1-phenylpropene [(3a) and (4a)], *cis*- and



(3) (5) (7)

(4) (6) (8)

a; R = Me b; R = Ph c; R = Bu^t

SCHEME 2

trans-stilbene [(3b) and (4b)], and *cis*- and *trans*-β-t-butylstyrene [(3c) and (4c)] with hydrogen fluoride–pyridine–NBS in ether at 15 °C (Scheme 2). The *trans*-olefins (4a—c) each gave only one isomer (6a—c). The structures of the products were assigned from the compounds formed when the bromo-fluorides (6a—c) were treated with base under conditions suitable for *trans*-elimination. The products [*cis*-1-fluoro-1-phenylalkenes (8a—c)] were identified on the basis of their n.m.r. spectra (J_{FH} 22 Hz).

This chemical transformation indicates that in the reaction with *trans*-olefins only (±)-*erythro*-2-bromo-1-fluoro-1-phenylalkanes are formed. [Although the terms '*erythro*' and '*threo*' are not strictly applicable, they will be used so that the stereochemistry of bromofluoride formation can be related directly to that of dibromide or difluoride formation.] However in the bromofluorination of the *cis*-olefins (3a and b), large amounts of both (±)-*erythro*- (6) and (±)-*threo*-2-bromo-1-fluoro-1-phenylalkanes (5) were formed. When mixtures containing (5a) and (6a) (65 : 35) or (5b) and (6b) (30 : 70) were treated with base under conditions suitable for *trans*-elimination, *trans*- (7a and b) and *cis*-1-fluoro-1-phenylolefins (8a and 8b) were formed in the ratios 65 : 35 and 30 : 70, respectively. This shows that the major isomer in the case R = Me is the (±)-*threo*-adduct (5a), and in the case R = Ph, the *erythro*-adduct (6b). Bromofluorination of *cis*-β-t-butylstyrene yields a product (6c) which was converted under basic conditions into the *cis*-fluoro-olefin (8c). The product distribution in the bromofluorination of the 1-phenylalkenes (3) and (4) is given in Table 1. Since the *cis*- and *trans*-1-phenylethylenes (3) and (4) give different product compositions, the products are not interconverted under the reaction conditions. In a control experiment, a mixture of known amounts of adducts (6) and (5) was added to ether containing hydrogen fluoride–pyridine and the solution was left for longer than the usual reaction period. The composition of the mixture was unchanged. It thus appears that the product distribution of Table 1 is the result of kinetic control. In all these additions no isomerisation of starting *trans*-olefins occurred during the addition, as evidence by both g.l.c. and n.m.r. analyses. On the other hand, isomerisation of the *cis*-olefins occurs to the extent of 10—60%; this must be taken into account when interpreting the results in Table 1.

The mechanism of electrophilic addition of bromine to alkenes has been extensively investigated, from both kinetic and stereochemical points of view.[7,9] It is now known that the nature of the intermediates [10-19] depends on the structure of the substrate and on the reaction medium, ranging from a strongly bridged bromonium ion of type (A) to a weakly bridged species of type (B), or an open-chain ion like (C) (Scheme 3). Whereas intermediates of type (A) are involved in bromination of non-conjugated olefins, which give only *anti*-adducts, in the case of aryl-substituted compounds the unsym-

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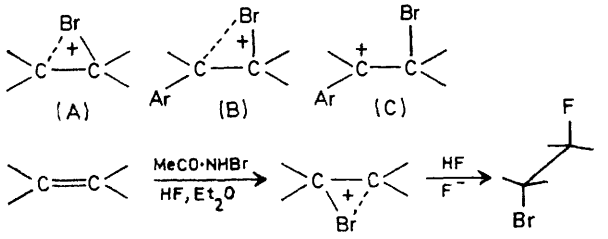
metrical bridged (B) or open species (C) must be involved to rationalise the nonstereospecific course of the addition, which leads to *syn*- as well as *anti*-adducts.



SCHEME 3

The stereochemical results of bromination reactions (Table 2) can be explained in terms of an intermediate

TABLE 1

Product distribution in the bromofluorination of substituted 1-phenylethylenes (3) and (4)

Olefin		Products [a] (%) (±)-*threo* (5)	(±)-*erythro* (6)
cis	(3a) [b]	65	35
	(3b) [c]	30	70
	(3c)		65
trans	(4a)		70
	(4b)		62
	(4c)		58

[a] Total yields after purification by t.l.c. [b] Relative yields determined by n.m.r. analysis; total yield 70%. [c] Total yield 61%.

TABLE 2

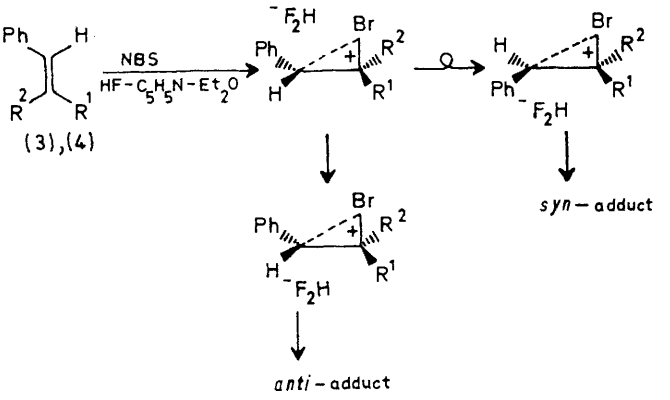
Stereochemistry of bromine addition to 2-alkyl-substituted styrenes

Olefin	Products (%) (±)-*threo*	(±)-*erythro*	Ref.
(3a)	83	17	14
(3c)	37.7	62.3	19
(4a)	12	88	14
(4c)	12.7	87.3	19

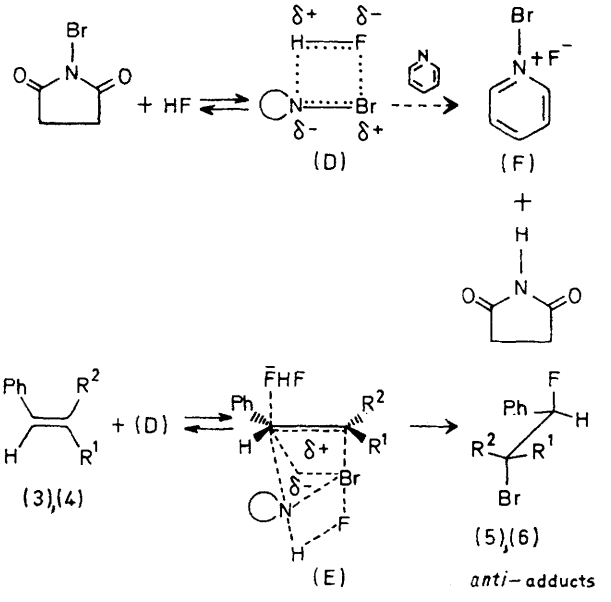
cis- or *trans*-stilbene in solvents of low polarity was found to undergo 90—100% stereospecific *trans*-addition.[15]

more resembling an open benzylic cation (C) than a bridged bromonium ion [19] (B).

For bromofluorination with *N*-halogeno-amides in the presence of hydrogen fluoride, the reaction sequence shown in Scheme 3, involving a cyclic bromonium ion, has been suggested.[2,3,20] The consequences of a mechanistic pathway involving an open bromium or a partly bridged bromonium cation are presented in Scheme 4. Were such an intermediate really involved, we should observe nonstereospecific addition. Our results (Table 1) show a stereospecific *anti*-addition for *trans*-olefins (4) and a nonstereospecific process for *cis*-olefins (3), which could be explained by the large extent of isomerisation of *cis*-olefins under the reaction conditions. Solvent polarity has been considered as the main factor affecting the extent of bridging in the intermediate, and consequently, the stereochemical results of bromination of the conjugated substrate.[15,16] However, the ability of the solvent to co-ordinate with the attacking electrophile and to solvate cationic intermediates must be also taken into account.[11] Little is known about the effect of hydrogen fluoride on the carbocations and there is the possibility of a more rigid bromonium ion, which can be attacked in the *anti*-position. Changes in the solvent polarity have little significant influence on the stereochemistry of bromination of *trans*-olefins, but are



SCHEME 4



SCHEME 5

reflected by loss of stereoselectivity in bromination of *cis*-olefins.

We suggest a more reasonable reaction pathway (Scheme 5), which can better explain the *anti*-stereoselectivity. We propose the formation of the polarised NBS–hydrogen fluoride complex (D), which reacts in a reversible step with the olefins (3) and (4) to form a transition state (E); this decomposes in the next step to products [(5) or (6)]. The reversible step in the formation of the transition state (E) could explain the high degree of isomerisation of *cis*-olefins under the reaction conditions.

[20] R. D. Chambers, ' Fluorine in Organic Chemistry,' Wiley, New York, 1973, p. 57.

A transition state similar to (E) was suggested for the bromination of 1-phenylcyclohexene with bromine–pyridine complex [21] and has also been proposed for *E*2Hal elimination of bromine from *trans*-1,2-dibromocyclohexane with benzenethiolate as base.[22] A polarised complex of NBS with olefins has been suggested in the bromination of styrene and cyclohexene with NBS in the presence of dimethyl sulphoxide and methanol.[23]

A third interpretation of the present reaction bromofluorination involves formation of a pyridinium–bromide complex (F), reacting with alkenes with high stereoselectivity. This complex (F) is probably involved in bromofluorination by bromine–hydrogen fluoride–pyridine [6] which results in bromofluorides accompanied by dibromides.

EXPERIMENTAL

I.r. spectra were recorded with a Perkin-Elmer 257 spectrometer, and ^1H and ^{19}F n.m.r. spectra with a JEOL JNM-PS-100 (CCl_4 as solvent and Me_4Si or CCl_3F as internal reference).† Mass spectra and high resolution measurements were obtained with a CEC-21-110 spectrometer. G.l.c. was carried out with a Varian Aerograph 1800 instrument and t.l.c. with Merck chromatoplates (PSC-fertigplatten Aluminiumoxid F-254-typ T).

Materials.—A solution of pyridine in hydrogen fluoride was prepared according to Olah's procedures.[6] Pyridine was distilled, and hydrogen fluoride (Fluka, Purum) was used without further purification. NBS (Fluka, Purum) was crystallised and dried (P_2O_5) before use. Diethyl ether was purified by standard methods and distilled before use. Pure samples of olefins were prepared by established methods: 1,1-diphenylethylene; [24] 1,1-diphenylpropene; [25] 2-fluoro-1,1-diphenylethylene; [26,27] 2-bromo-1,1-diphenylethylene; [27] 2-chloro-1,1-diphenylethylene; [27] *cis*-1-phenylpropene; [28] *trans*-1-phenylpropene; [29] *cis*-1-phenyl-2-t-butylethylene; [18] *trans*-1-phenyl-2-t-butylethylene.[18] Other olefins were commercially available and purified before use.

Addition and Isolation Procedures.—In a mixture of 70% hydrogen fluoride (2 ml) and ether (2 ml), NBS (250 mg 1.4 mmol) was dissolved with stirring at 0 °C, and then the olefin (1 mmol) was added. The mixture was stirred for 1 h at 15 °C [3 h for compound (2h)], then poured into ice–water and extracted with ether. The ether layer was washed with water, aqueous sodium hydrogen carbonate then water again, dried (Na_2SO_4), and evaporated. After purification by crystallisation or separation by preparative t.l.c. or g.l.c., n.m.r., mass, and i.r. spectra were taken. Yields and elemental analyses are presented in Table 3.

Bromofluorination of the *cis*- and *trans*-olefins (3) and (4) was repeated three times, and ^{19}F and ^1H n.m.r. spectra were also recorded for the crude reaction mixtures.

To test the stability of the bromofluorination products in the reaction mixture, a sample (0.25 g) containing (6a, b, or c) or the mixture of (5a) and (6a) (65 : 35) or (5b) and (6b) (30 : 70) was added to 70% hydrogen fluoride–pyridine (2 ml), ether (2 ml), and NBS (0.2 mmol) and the mixture was stirred at 15 °C for 1 h. After work-up the n.m.r. spectra showed no significant difference. By using mixtures of known composition it was demonstrated that no significant product fractionation occurred during isolation.

Isomerisation of Olefins under Reaction Conditions.—(i) The olefin (3) or (4) (1 mmol) dissolved in hydrogen fluoride–pyridine–ether (4 ml) was stirred at room temperature for 1 h. After adding water (15 ml), the product was extracted with ether and the extract was washed with aqueous sodium hydrogen carbonate, dried (K_2CO_3), and evaporated. G.l.c. of the crude product showed no significant isomerisation of the olefin.

(ii) In experiments in which a smaller amount (0.4, 0.5, or 0.6 mmol) of NBS and 1 mmol of olefin (3) or (4) were used under the same reaction conditions as those of bromofluorination, the unchanged olefins were analysed by g.l.c. No significant isomerisation of *trans*-olefins (4a—c) was observed but isomerisation of *cis*-olefins (3a—c) was in the range 10—60%. This high isomerisation must be taken into account when interpreting the results in Table 1.

Dehydrobromination of (±)-threo- (5) *and* (±)-erythro-*2-Bromo-1-fluoro-1-phenylalkanes* (6).—(i) The (±)-*erythro*-

TABLE 3

Yields and analytical data for 2-bromo-1-fluoro-1-phenylalkanes

Compd.	Yield (%)	Formula	Required % C	Required % H	Found % C	Found % H	*M*+ Calc.	*M*+ Found	M.p. (°C)
(2a)	77.5	$C_{14}H_{12}BrF$	60.2	4.35	60.45	4.55	278.010 69	278.010 70	59—61
(2b)	67.9	$C_{15}H_{14}BrF$	61.45	4.8	61.35	4.9	292.026 52	292.026 52	(Oily)
(2c)	63.6	$C_{14}H_{11}BrF_2$	56.55	3.75	56.25	3.8	296.001 26	296.001 93	(Liquid)
(2d)	55	$C_{14}H_{11}ClFBr$	53.6	3.55	53.65	3.3	311.971 71	311.971 75	63—64
(2e)	50	$C_{14}H_{11}Br_2F$	46.95	3.1	46.65	3.3	355.921 25	355.921 06	99
(2f)	53	C_8H_8BrF	47.35	3.95	47.25	4.1	201.979 39	201.979 31	(Liquid)
(2g)	72	$C_9H_{10}BrF$	49.8	4.65	49.4	4.8	215.995 04	215.995 04	(Liquid)
(2h)	49	$C_8H_7Br_2F$	34.1	2.5	33.75	2.8	279.889 95	279.889 79	(Oily)
(6a)	70	$C_9H_{10}BrF$	49.8	4.65	49.75	4.75	215.995 04	215.994 65	(Liquid)
(6b)	62	$C_{14}H_{12}BrF$	60.2	4.35	60.3	4.35	278.010 69	278.010 73	115—120
(6c)	58	$C_{12}H_{16}BrF$	55.6	6.2	55.85	6.5	258.041 98	258.042 55	(Liquid)

† N.m.r. data for the products (2), (5), and (6) are available as Supplementary Publication No. SUP 21675 (3 pp.). For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1975, Index issue.

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[29] V. J. Traynelis, W. L. Hergenrother, J. R. Livingston, and J. A. Valicenti, *J. Org. Chem.*, 1962, **27**, 2377.

product (6) (0.5 mmol) in M-potassium t-butoxide in t-butyl alcohol (2.5 ml) was stirred at 70 °C for 4 h, then cooled, mixed with water (15 ml), and extracted with methylene chloride. The extract was washed with dilute acid and water, dried ($MgSO_4$), filtered, and evaporated, and the residue was analysed by g.l.c. and n.m.r. spectroscopy. The *cis*-fluoro-olefin (8), the only product, was purified by preparative g.l.c.

(ii) A 63 : 35 mixture (0.5 mmol) of (5a) and (5b), in M-potassium t-butoxide in t-butyl alcohol, was stirred at 70 °C for 4 h, then cooled, mixed with water (15 ml), and extracted with methylene chloride. The extract was washed with dilute acid and water, dried ($MgSO_4$), filtered, and evaporated, and the residue was analysed by g.l.c. and n.m.r. spectroscopy. The product was a 35 : 65 mixture of (8a) and (7a). The two components were separated by g.l.c. on 12% didodecyl phthalate on Chromosorb (80—100 mesh) at 170 °C for (7a), (8a), and (8c); fluorostilbenes were separated on 10% Carbowax 20 M on Varaport 30 (70—80 mesh) at 180 °C.

N.m.r., i.r., and mass spectral data were in agreement with those reported [J_{FH} 22 Hz for *cis*- (8) and 37 Hz for *trans*-fluoro-olefin (7)].[30]

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