Effects of Remote Unsaturated Bonds at C-2 on Nucleophilic Aromatic Substitution of Fluorine in 6,7-Difluoro-1,2,3,4-tetrahydro-3,3-dimethyl-1,4-methanonaphthalenes

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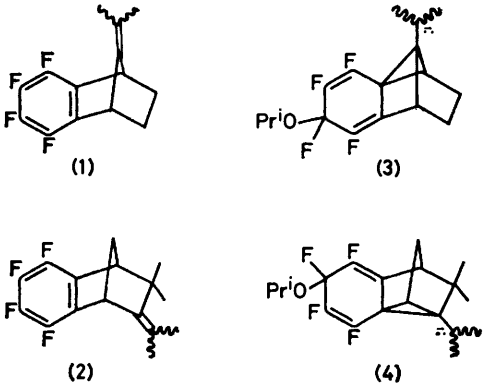
Approximate values of the second-order rate constant for fluorine replacement by isopropoxide ion in propan-2-ol–dimethyl sulphoxide (1 : 1 v/v) have been determined for a series of 6,7-difluoro-1,2,3,4-tetrahydro-3,3-dimethyl-1,4-methanonaphthalenes containing unsaturated groups at C-2. A factor of 13 separates the most reactive system [the 2-oxo compound (10)] from the least reactive [the 2-methylene compound (13)] but the lack of product regiospecificity excludes homoconjugation as a possible effect in stabilising the transition state for attack at C-6; the (*E*)-2-benzylidene compound (14) gave identical product ratios at 100 and at 150° in propan-2-ol.

In previous papers we have examined the effect of remote unsaturated bonds on the second-order rate constants for fluoride ion displacement by isopropoxide in 9-alkylidene-5,6,7,8-tetrafluoro-1,2,3,4-tetrahydro-1,4-methanonaphthalenes (1)[1] and in 2-alkylidene-5,6,7,8-tetrafluoro-1,2,3,4-tetrahydro-3,3-dimethyl-1,4-methanonaphthalenes (2).[2] Compared with related saturated compounds, only a small rate-enhancing factor of *ca.* 3—4 was observed in the most reactive systems, insufficient to warrant the proposition of homoconjugative interactions of types (3) and (4) in the respective transition state (Scheme). Only in one case have we found a significant rate enhancement,[2] in 5,6,7,8-tetrafluoro-1,4-dihydro-3,3-dimethyl-1,4-methanonaphthalen-2(3*H*)-one (5), where the carbonyl group at C-2 increased the second-order rate constant over the closely related saturated *endo*-2-methoxy compound (6) by a factor of 100 at 25°, but even here regiospecific homoconjugation at C-6 in the transition state was ruled out by the formation of similar amounts of C-6 and -7 substitution products. The field effect of the carbonyl group was proposed as the factor responsible for this rate enhancement, in which the ground state energy of (5) is effectively increased.



Scheme

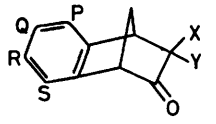
Recent studies using polyfluoroaromatic compounds have established that the site of nucleophilic substitution is that which has the maximum number of fluorine atoms in the *ortho*- and *meta*-positions,[3] and it was recognised in the case of the 9-alkylidene-5,6,7,8-tetrafluoro-1,2,3,4-tetrahydro-1,4-methanonaphthalenes that the rate constants for fluorine displacement at C-6 and -7 *could* be determined largely by the effects of the remaining three fluorine atoms and that any activation due to homoallylic conjugation might be being obscured.[1] Nevertheless, our investigation showed that the pattern of reactivity of the 6,7-difluoro compounds was similar to that found for the 5,6,7,8-tetrafluoro compounds, which indicated that (a) the remaining fluorine was controlling the pattern of reactivity even in the lightly fluorinated substrates and/or (b) homoconjugative interaction in the transition state is inoperative.

Olah has found recently that the π electrons of the aromatic ring in secondary 1,2,3,4-tetrahydro-1,4-methanonaphthalene systems overlap more effectively with a cationic centre generated at C-2 rather than one generated at C-9,[4] so that for our study it became imperative to examine substrates having both fewer fluorine atoms in the aromatic ring, *and* having the unsaturated group at C-2. In this paper we report on the products from, and reactivity of, fluorine displacement by isopropoxide ion in a series of 2-alkylidene-6,7-difluoro-1,2,3,4-tetrahydro-3,3-dimethyl-1,4-methanonaphthalenes and the corresponding 2-oxo compound.

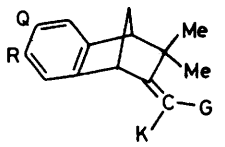
Syntheses.— 6,7-Difluoro-1,4-dihydro-1,4-methanonaphthalene (7), 6,7-difluoro-1,2,3,4-tetrahydro-1,4-methanonaphthalen-*exo*-2-ol (8), 6,7-difluoro-1,4-dihydro-1,4-methanonaphthalen-2(3*H*)-one (9), and 6,7-difluoro-1,4-dihydro-3,3-dimethyl-1,4-methanonaphthalen-2(3*H*)-one (10) were prepared by methods analogous to those described previously,[2] with the exception of (7) which employed a Grignard reagent rather than the lithium intermediate for generation of the aryne.

Treatment of the ketone (10) with methylmagnesium iodide and with benzylmagnesium chloride gave the tertiary alcohols (11) and (12) respectively (almost certainly the *endo*-alcohol by analogy with the earlier work). Reaction of (11) with thionyl chloride–pyridine gave the 2-methylene compound (13) while the analogous reaction with (12) gave a separable mixture of the (*E*)- and (*Z*)-2-benzylidene derivatives (14) and (15) respectively. The assignment of the stereochemistry is based on the positions of the vinylic proton resonances: that of the *z*-isomer (15) is more deshielded by the difluorobenzene ring.

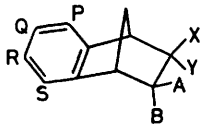
Unlike the isopropoxy-trifluoro compounds obtained by treatment of 5,6,7,8-tetrafluoro compounds with potassium isopropoxide, we were unable to differentiate 6-fluoro-7-isopropoxy compounds from the isomeric 7-fluoro-6-isopropoxy compounds derived from 6,7-difluoro compounds. Previously,[2] lanthanide-induced ^{19}F shift experiments with the alcohols (16) and (17) had established the *endo*-orientation of the hydroxy function and



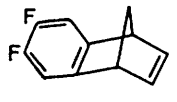
(5) P = Q = R = S = F; X = Y = Me
(9) P = S = H, Q = R = F, X = Y = H
(10) P = S = H, Q = R = F, X = Y = Me
(21) P = S = H, Q = OPr^i, R = F, X = Y = Me
(22) P = S = H, Q = F, R = OPr^i, X = Y = Me



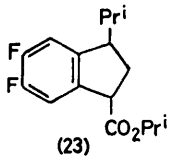
(13) G = K = H, Q = R = F
(14) G = H, K = Ph, Q = R = F
(15) G = Ph, K = H, Q = R = F
(27) G = H, K = Ph, Q = F, R = OPr^i
(28) G = H, K = Ph, Q = OPr^i, R = F
(25) G = H, K = H, Q = F, R = OPr^i
(26) G = H, K = H, Q = OPr^i, R = F



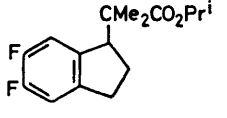
(6) A = H, B = OMe, P = Q = R = S = F, X = Y = Me
(8) A = OH, B = H, P = S = H, Q = R = F, X = Y = H
(11) A = Me, B = OH, P = S = H, Q = R = F, X = Y = Me
(12) A = CH_2Ph, B = OH, P = S = H, Q = R = F, X = Y = Me
(16) A = H, B = OH, P = R = S = F, Q = OPr^i, X = Y = Me
(17) A = H, B = OH, P = Q = S = F, R = OPr^i, X = Y = Me
(18) A = H, B = OH, P = S = H, Q = R = F, X = Y = Me
(19) A = H, B = OH, P = S = H, Q = OPr^i, R = F, X = Y = Me
(20) A = H, B = OH, P = S = H, Q = F, R = OPr^i, X = Y = Me



(7)



(23)



(24)

the position of the isopropoxy substituent because of easily distinguishable splitting patterns and the relatively rapid downfield shifts of the fluorine at C-8. In the alcohols (18) and the mixture (19) and (20) obtained by borane–tetrahydrofuran reduction of (10) and the mixture (21) and (22) respectively, the aromatic protons gave overlapping signals even with addition of shift reagent, and the fluorine substituents at C-6 and -7 did not shift downfield at rates sufficiently different to allow spectral assignment of the isomers. Nevertheless, isomer *ratios* could be obtained from the small differences in the ^{19}F shifts of the isomeric fluoro-isopropoxy compounds obtained from (10), (13), and (14).

The reaction of the ketone (10) with isopropoxide was complicated by the formation of a complex mixture in which the major component was the ring-opened material (23) [or (24)]. However, separation of the mixture by preparative t.l.c. enabled the amounts of (23) [or (24)], and a mixture of isopropoxy-fluoro ketones (21) and (22) to be determined, and by assuming pseudo-first-order kinetics for ring-opening and fluorine-substitution processes, we have estimated the second-order rate constant for substitution of fluorine by isopropoxide in (10).[5]

RESULTS AND DISCUSSION

Second-order kinetics are well established for the reactions of polyfluoroaromatic compounds with nucleophiles [3] and for the purpose of this present study we have assumed that these kinetics operate in our reactions and have calculated rate constants based on one determination of the percentage reaction after a given time. The kinetic data are summarised in the Table, together with that for *syn*-6,7-difluoro-1,2,3,4-tetrahydro-9-isopropyl-1,4-methanonaphthalene (29) [1] for comparison (in which there is no possibility of homoconjugation).

The pattern of reactivity is very similar to that found for the 5,6,7,8-tetrafluoro analogues,[2] and though the ketone (10) appears to be relatively less reactive, this is probably due to the gross assumptions which have had to be made in the calculations and the practical difficulty

of initiating the reaction at 100° when the reaction time is only 10 min. Consequently due to the heating-up

Second-order rate constants for reactions with potassium isopropoxide in propan-2-ol–dimethyl sulphoxide (1 : 1 v/v) at 100°

Compound	k/dm^3 mol^{-1} min^{-1}
(13)	0.0015
(14)	0.003 (0.002) [a]
(10)	0.02
(29)	0.0007

[a] Determined in propan-2-ol at 150°.

period, the actual reacting time will be less than 10 min, and the calculated rate constant will be less than its true value.

Significantly, however, mixtures of isopropoxy-fluoro isomers were formed in each case: 40 : 60 from (13); 33 : 66 from (14); and 50 : 50 from (10), so that, once again, regiospecific homoconjugation at C-6 is inoperative in spite of the difluoro system being rendered less active than the tetrafluoro system by a factor of *ca.* 9 000 [based on reactions of sodium methoxide in methanol with hexa-, penta-, and tetra-fluorobenzenes for the removal of one *ortho*- and one *meta*-fluorine (with activating effects of 56 and 167, respectively) [3] from the site of nucleophilic attack]. The relatively high rate of non-selective fluorine displacement in the ketone (10) is accountable in terms of the field effect of the carbonyl group proposed before.

It is now well established that in solvolysis reactions, solvent participation often competes very successfully against neighbouring group participation with the result that only small enhancements are observed with model compounds. A classical example concerns the $C_6H_5CH_2CH_2OTs : CH_3CH_2OTs$ rate ratio (Ts ≡ $SO_2C_6H_4CH_3$-*p*) which is 0.35 in acetic acid and 1 770 in trifluoroacetic acid, a non-nucleophilic solvent.[6] In the light of this we reduced the reactivity of one of our systems, the (*E*)-2-benzylidene compound (14) with potassium isopropoxide by carrying out the reaction in propan-2-ol at 150°. Even though this system was estimated to be less reactive than in the mixed solvent by a factor of *ca.* 300—400 if carried out at 100°, a product ratio of 33 : 66 for the isopropoxy-fluoro isomers was found, *identical* with that formed in the more reactive solvent, again indicating the absence of homoconjugation.

EXPERIMENTAL

^{1}H (90.00 MHz) and ^{19}F n.m.r. (84.67 MHz) spectra were obtained with a Brüker HX-90E spectrometer; fluorine absorptions are quoted in p.p.m. upfield from internal $CFCl_3$. For chemically induced shift experiments tris-(1,1,1,2,2,3,3-heptafluoro-7,7-di[$^2H_3$]methyl[8-$^2H_3$]octane-4,6-dionatoeuropium(III) {Eu([$^2H_9$]fod)$_3$} was used, the extrapolated induced shifts at 1 : 1 mole ratio {Eu([$^2H_9$]-fod)$_3$: substrate} being expressed as percentages of the H-2 shift change.

6,7-*Difluoro*-1,4-*dihydro*-1,4-*methanonaphthalene* (7).—A mixture of 1-bromo-2,4,5-trifluorobenzene (151.6 g) and cyclopentadiene (48.7 g) in anhydrous tetrahydrofuran (200 ml) was added to magnesium (17.5 g) [activated with 1,2-dibromoethane (0.5 ml)] in anhydrous tetrahydrofuran (55 ml) at such a rate as to maintain gentle reflux. The addition was completed after 30 min and the mixture was heated for a further 2 h, then cooled, diluted with aqueous hydrochloric acid, and extracted with ether. The extracts were dried ($MgSO_4$), the solvent evaporated, and the residue fractionally distilled to give the *alkene* (7) (88 g), b.p. 84.5° at 8 mmHg (Found: C, 73.9; H, 4.6. $C_{11}H_8F_2$ requires C, 74.15; H, 4.5%).

6,7-*Difluoro*-1,2,3,4-*tetrahydro*-1,4-*methanonaphalen*-exo-2-*ol* (8).—The alkene (7) was treated with borane–tetrahydrofuran and the product oxidised with hydrogen peroxide in sodium hydroxide solution as in the method described previously,[2] to give the exo-*alcohol* (8), m.p. 78.5—79.3° [from petroleum ether (b.p. 40—60°] (Found: C, 67.1; H, 4.85. $C_{11}H_{10}F_2O$ requires C, 67.35; H, 5.15%).

6,7-*Difluoro*-1,4-*dihydro*-1,4-*methanonaphthalen*-2(3H)-*one* (9).—The alcohol (8) was oxidised with *p*-benzoquinone and aluminium tri-t-butoxide in toluene as in the method described previously [2] to give the *ketone* (9), m.p. 49.0—50.5° [from petroleum ether (b.p. 40—60°)] (Found: C, 68.2; H, 4.2. $C_{11}H_8F_2O$ requires C, 68.05; H, 4.15%).

6,7-*Difluoro*-1,4-*dihydro*-3,3-*dimethyl*-1,4-*methano-naphthalen*-2(3H)-*one* (10).—The ketone (9) was subjected to the double methylation procedure described previously [2] to give the *ketone* (10), m.p. 99—100.5° [from petroleum ether (b.p. 60—80°)], $\delta_F(CDCl_3)$ 140.1 and 140.5 (not assigned) (Found: C, 70.25; H, 5.4. $C_{13}H_{12}F_2O$ requires C, 70.25; H, 5.45%). The ketone (10) was reduced with borane–tetrahydrofuran as before to give 6,7-*difluoro*-1,2,3,4-*tetrahydro*-3,3-*dimethyl*-1,4-*methanonaphthalen*-endo-2-*ol* (18), b.p. 85—86.5° at 0.01—0.05 mmHg (Found: C, 69.6; H, 6.4. $C_{13}H_{14}F_2O$ requires C, 69.65; H, 6.3%), $\delta_F(CDCl_3)$ 142.2 and 142.4; percentages of the H-2 lanthamide induced shifts 25 and 25(9-H_2).

2-*Methylene*-6,7-*difluoro*-1,2,3,4-*tetrahydro*-3,3-*dimethyl*-1,4-*methanonaphthalene* (13).—Treatment of the ketone (10) with excess methylmagnesium iodide in ether gave 2-*methyl*-6,7-*difluoro*-1,2,3,4-*tetrahydro*-3,3-*dimethyl*-1,4-*methanonaphthalen*-2-*ol* (11), b.p. 86—102° at 0.01—0.05 mmHg (Found: C, 70.85; H, 7.0. $C_{14}H_{16}F_2O$ requires C, 70.55; H, 6.75%). Treatment of the alcohol (11) in pyridine and carbon tetrachloride with thionyl chloride in carbon tetrachloride as described previously [2] gave the 2-*methylene compound* (13), b.p. 64° at 0.01—0.05 mmHg, $\delta_F(CDCl_3)$ 142.3 and 143.4 (unassigned) (Found: C, 76.15; H, 6.7. $C_{14}H_{14}F_2$ requires C, 76.35; H, 6.4%).

(E)- *and* (Z)-2-*Benzylidene*-6,7-*difluoro*-1,2,3,4-*tetrahydro*-3,3-*dimethyl*-1,4-*methanonaphthalene* (14) *and* (15).—Treatment of the ketone (10) with excess benzylmagnesium chloride as in the method described previously gave 2-*benzyl*-6,7-*difluoro*-1,2,3,4-*tetrahydro*-3,3-*dimethyl*-1,4-*methanonaphthalen*-2-*ol* (12), m.p. 86.5—88.5° [from petroleum ether (b.p. 40—60°)] (Found: C, 76.7; H, 6.1. $C_{20}H_{20}F_2O$ requires C, 76.4; H, 6.4%).

The alcohol in pyridine and carbon tetrachloride on treatment with thionyl chloride in carbon tetrachloride as described previously [2] gave the (E)-*benzylidene compound* (14), m.p. 102.5—103.5° [from petroleum ether (b.p. 40—60°)], $\delta_F(CDCl_3)$ 142.0 and 142.9 (unassigned); $\tau_H(CDCl_3)$ 3.83 (s, vinylic H) (Found: C, 81.25; H, 5.9. $C_{20}H_{18}F_2$ requires C, 81.05; H, 6.15%), which was separated by fractional crystallisation from the (Z)-*benzylidene compound* (15), m.p. 77.0—78.0° [from petroleum ether (b.p. 40—

60°)]; $\tau_H(CDCl_3)$ 3.4 (s, vinylic H) (Found: C, 81.15; H, 6.25%).

Reactivity Data. Reactions of 6,7-Difluoro Compounds with Potassium Isopropoxide in Propan-2-ol–Dimethyl Sulphoxide (1 : 1 v/v).—The approximate values of the second-order rate constants (Table) were determined as in the following typical experiments.

(a) The ketone (10) (0.225 4 g) and alkoxide solution (10 ml; 0.382M) were heated together in a sealed tube for 10 min at 100°. The mixture was diluted with water, extracted with ether, and the dried ($MgSO_4$) extracts evaporated. Preparative t.l.c. on silica [chloroform–carbon tetrachloride (60 : 40 v/v) as eluant] gave three fractions: (i) the ring-opened ketone {*i.e.* the *isopropyl ester* (23) [or (24)]} (0.140 1 g), b.p. 80—100° at 0.01—0.05 mmHg; $\delta_F(CDCl_3)$ 141.1 and 141.9 (unassigned) (Found: C, 68.15; H, 7.35. $C_{16}H_{20}F_2O_2$ requires C, 68.05; H, 7.15%); (ii) unchanged ketone (10) (0.045 2 g); and (iii) a 1 : 1 mixture of 6-fluoro-7-isopropyl- and 7-fluoro-6-isopropoxy-1,4-dihydro-3,3-dimethyl-1,4-methanonaphthalen-2(3*H*)-one (22) and (21) (0.015 8 g), b.p. 110—125°; $\delta_F(CDCl_3)$ 134.8 and 135.2 (unassigned) (Found: C, 73.25; H, 7.3. Calc. for $C_{16}H_{19}FO_2$: C, 73.25; H, 7.3%). Reduction of the mixture of (21) and (22) gave the mixture of alcohols (19) and (20) (Found: M^+, 264. Calc. for $C_{16}H_{21}FO$: *M*, 264).

(b) The (*E*)-2-benzylidene compound (14) (0.203 4 g) was treated with isopropoxide (6.8 ml, 0.364M) for 1 057 min at 100° and the product, examined by ^{19}F n.m.r. spectroscopy, showed the formation of fluoro-isopropoxy compounds to the extent of 65%, giving the calculated second-order rate constant 3×10^{-3} dm^3 mol^{-1} min^{-1}. Preparative t.l.c. on silica using chloroform–carbon tetrachloride (1 : 1 v/v) as eluant gave a mixture of (*E*)-2-benzylidene-6-fluoro-1,2,3,4-tetrahydro-7-isopropoxy-3,3-dimethyl-1,4-methanonaphthalene (25) and the 7-fluoro-6-isopropoxy isomer (26), m.p. 97.5—99° [from petroleum ether (b.p. 40—60°)]; $\delta_F(CDCl_3)$ 136.0 and 136.7 (unassigned) in the ratio 1 : 2 (Found: C, 81.85; H, 7.7. Calc. for $C_{23}H_{25}FO$: C, 82.1; H, 7.5%).

(c) The 2-methylene compound (13) was treated with isopropoxide as in (b) giving a mixture of 2-methylene-6-fluoro-1,2,3,4-tetrahydro-7-isopropoxy-3,3-dimethyl-1,4-methanonaphthalene (27) and the 7-fluoro-6-isopropoxy isomer (28), b.p. 94—98° at 0.05—0.01 mmHg; $\delta_F(CDCl_3)$ 136.2 and 137.5 (unassigned) in the ratio 2 : 3 (Found: C, 78.7; H, 8.0. Calc. for $C_{17}H_{21}FO$: C, 78.4; H, 8.15%).

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