ANODIC OXIDATION OF p-DISUBSTITUTED BENZENES IN THE PRESENCE OF FLUORIDE ION

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Abstract—Electrochemical oxidation of aromatic compounds in the presence of fluoride ion gives products derived from initial oxidation of aromatic substrate and subsequent reaction with fluoride ion. The second of the one-electron transfer steps leads to benzenium ions, which give either fluoroaromatic compounds (elimination) or fluoro-cyclohexadienes (addition). The elimination of a t-butyl-group during anodic oxidation of p-di-t-butylbenzene, yielded p-fluoro-t-butylbenzene. Further examples of the reaction involve p-fluorodiphenyl, p-fluoro-t-butylbenzene, and p-fluorophenol ethers.

We have shown earlier that anodic oxidation of aromatic compounds in the presence of fluoride ion leads to fluorine containing compounds.¹⁻⁵ The oxidation scheme was postulated as an ECEC (electrochemical-chemicalelectrochemical-chemical) process. The primary oneelectron transfer is followed by the chemical reaction with fluoride and a second electron transfer occurs at the same electrode potential. The generated benzenium ion (1) may react further in two pathway (see Fig 1): (a) the proton elimination producing fluoroaromatic compounds takes place when a tetrahedral carbon of 1 bonded with hydrogen (X = H); (b) the addition of a second fluoride ion producing difluoro-cyclohexa-1,4-diene 2 takes place when X = F or C₆H₃.¹⁶

In this paper we wish to describe some different routes of chemical reaction of benzenium ions generated by anodic oxidation of p-disubstituted aromatic compounds in the presence of fluoride ion.

[†]The possibility of the anodic replacement of t-butyl-group by pyridine has been demonstrated recently by Popp⁷ for trit-butylphenol.

RESULTS AND DISCUSSION

Oxidative replacement of t-butyl group by fluoride ion

The anodic oxidation of p-di-t-butylbenzene 3 in tetraethylammonium trihydrogentetrafluoride (TEAF) in CH₃CN leads to replacement of one t-butyl-group by fluoride ion at anode potential of 1.75 v (versus Ag/Ag⁺ 0.1 M in CH₃CN). The main product of the reaction was pfluoro-t-butylbenzene 4. Similar replacement of t-butylgroup also occurs with p-t-butyltoluene 5, giving pfluorotoluene.[†] The reaction scheme (Fig 2) involves elimination of a t-butyl-cation from a benzenium ion 6 generated electrochemically. The eliminated t-butylcation reacts with CH₃CN to give N-t-butylacetamide (Ritter reaction). The rate of elimination appears to be high which explains why 6 does not react with fluoride ion. The poor yield of p-fluorotoluene in the case of 5 may be accounted for by predominant competitive proton loss from a methyl group of cation radical $\mathbf{8} \mathbf{R} = \mathbf{CH}_3$. As a result of further oxidation, the benzyl cation is formed which reacts along another pathway. Such oxidation schemes have been demonstrated earlier for methylbenzenes."



Fig. 1



Oxidative 1,4-addition

In contrast to compound 3 the oxidative replacement of a t-butyl-group by fluoride for p-fluoro-t-butylbenzene 4 occurs to a very small extent (5%). Instead, the predominant product of anodic oxidation 4 in TEAF solution in CH₃CN was N-(1-t-butyl-4,4difluorocyclohexa-2,5-dienyl)-acetamide 9, a result of 1,4-fluoroacetamidation.



electron transfer (Table 1).

At first sight the formation of 9 indicates the unusual reactivity of intermediate cationic species generated by anodic oxidation of 4. One could suppose the nucleophilicity of CH₃CN would be greater than that of H₃F₄. The "greater" nucleophilicity of CH₃CN as compared with H₂O and acetate anion has been observed upon anodic oxidation of methylbenzenes in H2O-CH3CN° and in CH3COOH-CH3CN.10 The main products of these reactions were corresponding benzyl acetamides. Nevertheless, it was shown later that the detailed oxidation mechanism is markedly dependent on pH and exhibits complications due to several coupled chemical reactions.

We suppose the formation of amide 9 to be a result of subsequent reaction of the initially generated trifluorocyclohexadiene 10 with CH_3CN . This is for the most part due to the different degrees of stability of 9 and 10 in acid media. The following mechanism is postulated for the anodic oxidation of 4 (Fig 3).

According to this ECEC-scheme 4 gives cations 12 and

 † The ability of alkyl fluorides to react with CH₃CN in HF solution has been shown recently.¹²

The fates of cations 12 and 13 differ; 13 rapidly eliminates a t-butyl-cation (like 6) to give pdifluorobenzene. 12 adds a second fluoride ion to give trifluorocyclohexa-1,4-diene 10. However, this addition appears to be reversible in acidic medium and therefore 12 reacts irreversibly with CH_3CN to give the imidoylfluoride 14[†]. This compound was detected by ¹⁹F NMR of the solution immediately after the electrolysis, based on the typical signal of -CF=N- group.

13 after reaction with fluoride coupled between two

charge transfers. The attack of cation radical 11 by $H_3F_4^$ anion is controlled by the charge density distribution in

this intermediate. The attack is directed predominantly to

carbon atom C-1 (total positive charge +0.412) to lead to cation 12 and to a smaller extent to carbon atom C-4 (total

positive charge +0.169 giving cation 13 after the second

Finally, the formation of 9 is in good agreement with the INDO calculated charge density distribution of 12, because the electrophilic reaction centre is localized definitely at carbon atom C-4 (see Table 1).

The lability of an allylic fluorine atom is observed also for amide 9. However, it needs catalysis by a stronger acid. Thus, dissolving 9 in CF₃COOH causes the elimination of fluorine and t-butyl-group.

A benzylic fluorine atom is also unstable in acidic media. For example, anodic oxidation of p-fluorotoluene 7 in a solution of TEAF in CH₃CN gives an exclusive attack at a methyl group and produces N-(p-fluorobenzyl)-acetamide in 60% yield. In this case fluoride addition to benzylic cation is also reversible.





Fig. 3

density distribution for 11 and 12 10 10 Total charge Total charge Atom density of 11 density of 12 1 0.412 0-497 2 -0.0070.088 3 0.055 -0.020 4 0.169 0.267 5 6 7 0.055 -0.020 -0.007 0.088 0.035 0.048 8 0.044 0.043 9 0.0740.074 0.044 0-043 10 F -0.129 -0.193

Table 1. INDO calculations of charge

Nevertheless, in some compounds both benzylic and allylic fluorine atoms in acid medium are stable enough to exclude the subsequent reaction with CH₃CN. It is possible to isolate the products of initial reactions of cationic species with fluoride ion. Such stability is the case for those fluorocyclohexadienes which contain fluorine atoms either in CF_2 -group or in CF--C₆H₅ group.^{1,3,6} For instance, anodic oxidation of pfluorodiphenyl 15 in CH₃CN solution of TEAF gives 3phenyl-3,6,6-trifluorocyclohexa-1,4-diene (16). 16 is quite stable enough to be isolated by rapid pentane extraction after electrolysis.

The fluoride attack on cation radical 17 (see Fig 4) and cation 18 by fluoride ion is directed to the carbon atoms bearing the most positive charge (see Table 2).

Anodic oxidation of p-fluorophenol ethers

Anodic oxidation of p-fluoroanisole (19) and pfluorophenetol (26) in TEAF solution in CH_3CN leads to addition of one fluoride ion and a cleavage of the O-alkyl bond, giving 4,4-difluorocyclohexa-2,5-dienone (21). The oxidation scheme (see Fig 5) consists of the initial oxidation of 19 or 20, the subsequent reaction of cation radical 22 with fluoride coupled with a second electron transfer to give cation 23. Then 23 either adds reversibly fluoride ion or eliminates irreversibly an alkyl cation giving 21 (see Fig 5). Fluoride ion attack on 23 and 22 follows at the carbon atoms bearing the most positive charge (see Table 3). The loss of alkyl cation from cation radical 22 is less probable because the diketal of





Fig. 5

Table 2. INDO calculations of charge density distribution for 17 and 18



Atom	Total charge density of 17	Total charge density of 18
1	0.393	0.505
2	-0.033	0.099
3	0.075	-0.013
4	0.095	0.238
5	0.075	-0.012
6	-0.033	0.029
7	0.073	>-0·007
8	0.052	0.075
9	0.049	0.042
10	0.087	0.128
11	0.049	0-014
12	0.02	0.079
F	-0.123	-0.214

Table 3. INDO calculation of charge density distribution for 22 and 23



Atom	Total charge density of 23	Total charge density of 22
1	0.414	0.157
2	0.037	0.049
3	0.094	-0.051
4	0.495	0.376
5	0.104	-0.031
6	0.053	0.079
7	0.257	0.202
F	0.190	-0.172
0	-0.155	+0.021

radicals 11, 17, 23 and for benzenium ions 12, 18, 22 by INDO semiempirical method¹⁴ with TOREAMOR program¹⁵ on a BESM-6 computer. Standard bond distances and angles were used. For example, the C-F distance was taken 1.30 Å in cation radicals and 1.36 Å in CF₂-group with F-C-F angle being 108°. The plane of CF₂-group was perpendicular to the ring plane. Generally, the ring geometry was accepted to be planar. The charge density distributions (see Tables 1, 2 and 3) are given for total charges.

p-benzoquinone was obtained upon anodic oxidation of p-dimethoxybenzene in methanol solution without any dealkylation.¹³ The allylic fluorine atoms in 21 are quite stable towards replacement.

CALCULATION

MO calculation have been carried out for cation

EXPERIMENTAL

¹⁹F NMR spectra were recorded on a H-60 Hitachi spectrometer, PMR spectra on a R12 Perkin-Elmer spectrometer. Chemical shifts are in ppm (δ), from CF₃COOH and TMS (external standards), J are in Hz. IR spectra were recorded on a UR-20 spectrometer (values in cm⁻¹). Mass spectra were obtained on a CH8 Varian spectrometer (70 eV). GLC analyses were carried out using 3 m column (10% Reoplex-400 on Chezasorb AW) at 80°C and 130°C. The internal standard method was used for estimation of quantity of a compound obtained upon electrolysis (accuracy ±3%).

Electrochemical procedure. General. All the experiments were performed using smooth platinum electrodes in an undivided three-electrode cell. The cell was a Teflon parallelepiped (11×65 mm with height 110 mm), the distance between plate electrodes (65 × 60 mm) was 10 mm. To stir the solution a suction pump was used with a sucker step 2 cm³ at 100 cycles/min. All the electrolyses were carried out in an atmosphere of dry argon with a pulse change of controlled potential (50 sec at the potential of interest and 10 sec at 0 V). Reference electrode was Ag/AgNO, (0.1 M) in dry CH₃CN. Generally, the electrolyses were performed at anode potential near above the oxidation half-wave potential of the aromatic substrate. Aromatic substrate was dissolved in 60 ml of 0.7 M solution of TEAF in dry CH₃CN. The initial current density was about 1×10^{-2} A/cm² and 1×10^{-3} A/cm² at the end of the electrolysis. To estimate the current passed a Cu-coulometer was used (accuracy ±5%).

Tetraethylammonium trihydrogentetrafluoride (TEAF). 130 g of tetraethylammonium iodide was added to a 800 ml anhydrous HF at 15° in a Teflon flask. The solution was evaporated at 20° and 6 h at 160°, then dried over P_2O_5 for 20 h at 1 mm to give 95 g white hygroscopic crystals of TEAF. (Found: F, 36.5. CaH23F4N requires: F, 36.36%).

p-Fluoro-t-butylbenzene 4. 50 g t-butanol was added to a stirred solution of 75 g fluorobenzene in 100 ml of anhydrous HF at 0-20° (1 h). The mixture was poured on ice, upper layer separated, washed with H₂O, dried and distilled to yield 52 g (40%) of 4, bp 172°, n_D²⁰: 1.4725.^{16,17}

Anodic oxidation of p-di-t-butylbenzene 3. 4.2 g of 3 were electrolyzed at 1.70 V until 2.2 F/mol of electricity was passed. The solution was poured into 200 ml H₂O, extracted with pentane $(8 \times 10 \text{ ml})$, then with CHCl₃ (6 × 20 ml). Distillation of the pentane extract gave 2.1 g (63%) of 4 found to be identical in all respects with that produced from the alkylation of fluorobenzene. From the CHCl₃ extract 0.8 g of butylacetamide was isolated, mp 95° (hexane).⁷

Anodic oxidation of p-t-butyltoluene 5. 3.5 g of 5 were electrolyzed at 1.80 V until 2.0 F/mol was passed and the solution was extracted with pentane (6×15 ml). After careful distillation of pentane the rest was studied by GLC at 130° and ^{1°}F NMR technique and found to contain 0.12 g of 7.

Anodic oxidation of p-fluoro-t-butylbenzene 4. (a) 2.2 g of 4 were electrolyzed at 2.0 V until 1.4 F/mol was passed. The solution was poured into 200 ml H₂O, white precipitate was filtered off to yield 2.0 g 9, mp 126° (methanol). IR: 3328, 1660 cm⁻¹; mass: m/e 229 (M⁺), 214 (M⁺-CH₃), 173 (M⁺-C₄H₈), 153 $(M^*-C_4H_5F, FC_4H_3NHCOCH_5^*)$, 111 (153–CH₂CO), 80-5 (153–111), 57 (C_4H_5^*), 43 (CH₃CO^{*}). The ¹⁹F NMR spectrum with computer of average transients (DMF, satd.): XY-part of AA'BB'XY-system; (-CH=CH)₂CF₂; $A_1A' = H$; $B_1B' = H$; X,Y =F. $\delta_x 2.45$, $\delta_y 6.05$, $J_{xy} = 305$ Hz, $J_{Bx} = 4.5$ Hz, $J_{By} = 6.0$ Hz. PMR spectrum: δ 1·1 (S, 9H, (CH₃)₃C); δ 2·0 (S, 3H, CH₃CO); 4 H ring, 9 lines, AA'BB'-part of AA'BB'XY system, δ_A , $\delta_{A'}$ 6.73, δ_B , $\delta_{B'}$ 6.32, $J_{AB} = 10.5$ Hz, $J_{Bx} = 4.5$ Hz, $J_{By} = 6.0$ Hz. (Found: C, 62.27; H, 7.52; F, 16.42; N, 6.01. $C_{12}H_{17}F_2ON$ requires: C, 62.90; H, 7.42; F, 16.59; N, 6.12%). The ¹⁹F NMR spectrum of the solution of 0.2 g 9 in 3 ml CF₃COOH showed a signal at 41.3 ppm attributed to

p-fluoroacetanilide. After adding H2O, white crystals were isolated, mp 151° (subl.).¹

(b) 1.5 g of 4 were electrolysed as above. The solution was concentrated in vacuo. The ¹⁹F NMR spectrum of the residue showed signals at 4.0 ppm (CF₂) and -70 ppm (CH₃-CF=N-) ascribable to 14. The treatment of the rest with H₂O resulted 9, mp 126° (methanol). The distillate collected in a trap (-70°) contained (GLC at 80°) 0.06 g of p-difluorobenzene.

Anodic oxidation of p-fluorotoluene 7. 4.3 g of 7 were electrolyzed at 2.0 V until 0.8 F/mol was passed. The solution was poured into 200 ml H₂O and unreacted 7 (3.0 g) was separated. The ether extraction of solution gave 1.2 g (62%) of N-p-fluorobenzylacetamide, mp 102° (subl.). The ¹⁹F NMR spectrum (CH₃COCH₃): 41-0. (Found: C, 64-36; H, 6-34; N, 8-11. C₉H₁₀FON requires: C, 64.55; H, 6.01; N, 8.38%).

Anodic oxidation of p-fluorodiphenyl 15. 1.8g of 15 were electrolyzed at 1.5 V until 2.2 F/mol was passed. The solution was extracted with pentane (10×30 ml). The distillation of the pentane extract gave 1.4 g of a mixture of 16 and 15, bp 47-50° at 1×10⁻⁴ mm. (Found: C, 71·21; H, 4·47; F, 23·58. C₁₂H₉F₃ requires: F, 27.14. C₁₂H₉F requires: F, 11.04%). To this mixture a quantity of C₆H₅F was added as an internal standard for ¹⁹F NMR. The mixture contained 1.1 g of 16 (in yield 63%) and 0.3 g of 15. The ¹⁹F NMR spectrum (CCL): 16, ABX-system, δ_A 8-16, δ_B 14-0, $J_{AB} = 310 \text{ Hz}, 2\text{F}; \delta_x 75.5, 1\text{F}; 15, 37.5 (3t, \text{F}).$ 16 is unstable and decomposes with evolution of HF even when kept in dry argon in a glass tube.

Anodic oxidation of p-fluoroanisole 19. 2.3 g of 19 were electrolyzed at 1.4 V until 1.3 F/mol was passed. The solution was poured into 150 ml H₂O and extracted with pentane (6×10 ml). The extract was cooled (-70°) , filtered off and gave 1.2 g of 21 (50%) as pale-yellow volatile crystals, mp 74.5-75° (subl). IR: 1695, 1645 cm⁻¹. UV (pentane): λ 248 nm, ε 3300. The ¹⁹F NMR: δ 19.1, J_{HF} = 4.95 Hz (t). PMR: 4 H ring, AA'BB' part of AA'BB'X₂ system, 7 lines, δ_A , $\delta_{A^{\dagger}}$ 6.23, $\delta_B = \delta_{B^{\dagger}}$ 6.73, $J_{AB} = 9.74$ Hz, $J_{BX} = 4.95$ Hz.

Anodic oxidation of p-fluorophenetole 20. 2.8 g of 20 were electrolyzed at 1.35 V until 1.5 F/mol was passed. The similar treatment gave 1.2 g of 21, mp 75°.

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