Direct Liquid-Phase Fluorination of Aromatic Compounds[1]

V. GRAKAUSKAS

Environmental Systems Division, Aerojet-General Corporation, Azusa, California 91702

Received April 29, 1969

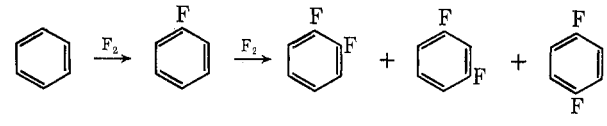
Direct liquid-phase fluorination of benzene, toluene, nitrobenzene, methyl benzoate, naphthalene, and several other aromatic compounds gave the corresponding aromatic monofluoro and polyfluoro derivatives. An ionic electrophilic substitution mechanism is proposed for these reactions on the basis of distribution of *o*-, *m*-, and *p*-fluoro isomers of monosubstituted fluorobenzenes. Under exhaustive fluorination conditions, the substitution products produced during the early stages of fluorination were consumed in addition and polymerization reactions, yielding low molecular weight, highly fluorinated polycyclohexene derivatives.

Recently, we reported[2] that direct liquid-phase fluorination of halogenated aromatic compounds, *e.g.*, trichlorobenzene, proceeds *via* addition and polymerization, yielding the corresponding 1,2,3,4,5,6-hexafluorocyclohexane derivatives and/or polytetrafluorocyclohexenes. In one instance, in the fluorination of *o*-dichlorobenzene, substitution in the aromatic nucleus was observed. This paper deals with aromatic substitution reactions under direct liquid-phase fluorination conditions.

Aromatic fluorine compounds are prepared[3] by a nucleophilic halogen displacement, replacement of a primary amino group, by dehydrohalogenation or dehalogenation of chlorofluorocyclohexanes, or by cyclizing aliphatic fluoro compounds. The fluorination of aromatic compounds was accomplished with interhalogen fluorides and metal fluorides of higher valence. For example, chlorine trifluoride with silver, cobalt, or mercuric fluoride as catalysts gave low yields of fluorine derivatives with benzene, toluene, or chlorobenzene;[4] the major products were aromatic chlorine compounds.

Previous attempts to synthesize aromatic fluorine compounds by direct fluorination were unsuccessful and the failure was attributed to the great reactivity of fluorine resulting in very high heats of reaction.[5] Attempts to control these reactions by diluting fluorine with an inert gas were unsuccessful.[6] On the other hand, in our work on direct liquid-phase fluorination of urea,[7] carbamates,[8] aliphatic nitro compounds,[9] and, more recently, halogenated aromatic compounds,[2] no major problems were encountered with the control of the exotherm, and other workers employing the direct liquid-phase fluorination technique during the past several years concur with this observation.[10,11] The now numerous examples of successful direct liquid-phase fluorination of organic compounds suggested to us that direct substitution in an aromatic nucleus was overlooked by the earlier workers because of experimental problems.[12] With this objective in mind, a number of selected aromatic compounds were examined under direct liquid-phase fluorination conditions in a screening program.

The fluorination of benzene was investigated under a wide range of reaction temperatures, concentrations, and degrees of fluorination. The fluorination of a 6% solution in acetonitrile at −35° at a 0.7:1 molar ratio of fluorine to benzene yielded predominantly the substitution products. The reaction product, separated from a small amount of polymeric material, contained a mixture of benzene, fluorobenzene, and the three isomers of difluorobenzene.



The reaction products werec haracterized by nmr on the basis of the reported[13,14] fluorine nmr spectra. The approximate relative ratio of the products in the mixture was 1:4:5:60 for *m*-, *o*-, and *p*-difluorobenzene and fluorobenzene, respectively.

When the fluorination of benzene was carried out utilizing higher molar ratios of fluorine to substrate, smaller amounts of aromatic fluorine compounds and relatively larger amounts of polymeric products were obtained. Thus, for example, the fluorination of 7.8 g (0.1 mol) of benzene utilizing 0.4 mol of fluorine yielded 13 g of a viscous oil containing 63% fluorine. The fluorine nmr spectrum indicated that aromatic fluorine compounds were not present in the mixture. The spectrum exhibited a broad envelope at ϕ 180–220, characteristic of fluoroalkanes. The approximate empirical structure, $C_6H_4F_6$, and its physical properties, showed that this material was a mixture of highly fluorinated polycyclohexenes. The data also indicated that two consecutive reactions were operative in the fluorination of benzene: substitution, and addition and polymerization.

The relative ratio of the three difluorobenzene isomers obtained in the fluorination of benzene at a low fluorine to substrate ratio suggested that direct liquid-phase fluorination of aromatic compounds proceeds *via*

(1) Presented in part at the Fourth International Symposium on Fluorine Chemistry, Estes Park, Colo., July 1967.

(2) V. Grakauskas, *J. Org. Chem.*, **34**, 2835 (1969).

(3) The general discussion of synthetic procedures can be found in the following references: (a) A. E. Pavlath and A. J. Leffler, "Aromatic Fluorine Compounds," Reinhold Publishing Corp., New York, N. Y., 1962; (b) M. Stacy, J. C. Tatlow, and A. G. Sharpe, Ed., "Advances in Fluorine Chemistry," Vol. 2, Butterworths Scientific Publications, London, 1961; (c) A. K. Barbour and P. Thomas, *Ind. Eng. Chem.*, **58**, 48 (1966).

(4) J. F. Ellis and W. K. R. Musgrave, *J. Chem. Soc.*, **3608** (1950); 1063 (1953).

(5) Reference 3a, pp 2, 3.

(6) N. Fukuhara and L. Bigelow, *J. Amer. Chem. Soc.*, **60**, 427 (1938).

(7) V. Grakauskas, Abstracts, 140th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1961, p 23M.

(8) V. Grakauskas, Third International Symposium on Fluorine Chemistry, Munich, Sept 1965.

(9) V. Grakauskas and K. Baum, *J. Org. Chem.*, **33**, 3080 (1968).

(10) R. F. Merritt, *ibid.*, **32**, 4124 (1967).

(11) R. E. Banks, R. N. Haszeldine, and J. P. Lalu, *J. Chem. Soc., C*, 1514 (1966).

(12) Subsequent to the preliminary report of this work at the Fourth International Symposium on Fluorine Chemistry, Estes Park, Colo., July 1967, C. L. Coon, M. E. Hill, and D. L. Ross [*J. Org. Chem.*, **33**, 1387 (1968)] reported three additional examples of aromatic fluorine substitution.

(13) G. Filipovich and G. V. D. Tiers, *J. Phys. Chem.*, **63**, 761 (1959).

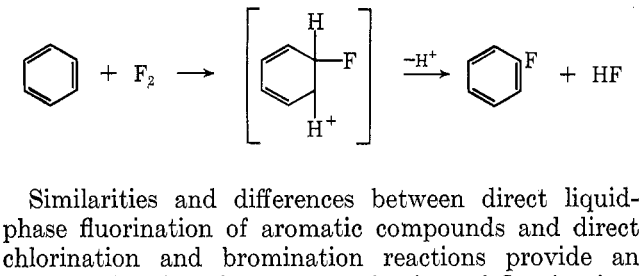
(14) H. S. Gutowsky, D. W. McCall, B. R. McGarvey, and L. H. Meyer, *J. Amer. Chem. Soc.*, **74**, 4809 (1952).

electrophilic substitution analogous to the ionic halogenation reactions of aromatic compounds.[15] In search for additional evidence in support of this probable reaction mechanism, the fluorination of toluene and nitrobenzene, which undergo electrophilic substitution predominantly in *ortho* and *para* positions and the *meta* postion, respectively, was examined next.

The fluorination of toluene using undiluted substrate at −70° at 0.7 mol of fluorine per 1 mol of toluene yielded a mixture of products. The fluorine nmr spectrum exhibited three signals at ϕ 114.8, 118.3, and 119, assigned to *m*-, *o*-, and *p*-fluorotoluene, respectively, on the basis of reported[14] nmr spectra. The approximate ratio of the three isomers in the mixture, estimated by integration of the nmr signals, was 1:5:4 for the *meta*, *ortho*, and *para* isomes, respectively. The fluorine analysis, 6.5% F, indicated that the mixture consisted of 62% unreacted toluene and 38% fluorotoluene isomers. The fluorination product mixtures of benzene and toluene were also analyzed by gas chromatography and the retention times of the isomers were compared with those of authentic samples (see Experimental Section for details).

The monomeric fraction obtained in the fluorination of nitrobenzene, amounting to *ca.* 90% of the total product, was analyzed by nmr. Its fluorine nmr spectrum exhibited signals at ϕ 103, 110, and 119.1, assigned to *p*-, *m*-, and *o*-nitrobenzene, respectively, on the basis of reported[14] fluorine nmr spectra. The relative areas of nmr signals showed that *p*-, *m*-, and *o*-fluoronitrobenzene isomers were present in a 1:9:1.5 ratio. The elemental analysis indicated that the mixture contained 40% unreacted nitrobenzene.

The ratio of *ortho*, *meta*, and *para* isomers observed in the fluorination of benzene, toluene, and nitrobenzene seems to indicate that direct liquid-phase fluorination of aromatic compounds proceeds by ionic electrophilic substitution represented in the following equation.



Similarities and differences between direct liquid-phase fluorination of aromatic compounds and direct chlorination and bromination reactions provide an additional insight into the mechanism of fluorination. Substitutions of chlorine or bromine in aromatic compounds in the presence of catalysts such as iron or ferric chloride are recognized as polar reactions,[15b] whereas the photochemical or peroxide-catalyzed additions to the nucleus proceed through a free-radical mechanism.[16] The distinction between the polar and free-radical mechanism is clear-cut and, in most cases, halogenations can be directed to give either type of product.[17-22]

One major difference between direct liquid-phase fluorination and other halogenation reactions of aromatic compounds lies in the formation of polymeric addition products in the former case. The analogous polymeric materials have not been observed in either the ionic or free-radical chlorination or bromination of aromatic compounds.

The similarities of direct liquid-phase chlorination, bromination, and fluorination of benzene, toluene, and nitrobenzene provided the basis for the proposed mechanism. The classical electrophilic substitution orientation rules observed in the fluorination of these three substrates as well as other compounds to be discussed later seem to indicate that direct liquid-phase fluorination of aromatic compounds proceeds by an ionic mechanism.

In addition to benzene, toluene, and nitrobenzene, discussed above, the fluorination of several other substituted benzenes and naphthalene was also investigated. In general, the fluorination of these compounds proceeded in an analogous manner to those already discussed. Some of the more pertinent observations regarding the fluorination of these substrates will be found in the subsequent discussion.

The fluorination of 2,4-dinitrotoluene was sluggish. The reaction product, obtained in *ca.* 5% yield, was characterized as 2,4-dinitro-6-fluorotoluene on the basis of fluorine and proton nmr spectra. The deactivating effect toward substitution exerted by the electronegative nitro substituents was apparent. The bromination of 2,4-dinitrotoluene to the 6-bromo derivative required concentrated sulfuric acid and silver sulfate catalyst.[23]

The fluorination of naphthalene proceeded in a manner analogous to that of mononuclear aromatic compounds. At low fluorine to substrate ratios, naphthalene yielded a mixture of α-fluoronaphthalene and β-fluoronaphthalene in a 3:1 ratio. Under exhaustive fluorination conditions, on the other hand, only polymeric products containing 60–65% fluorine were obtained.

The chlorination and bromination of naphthalene yield α-halo derivatives,[24-26] but β-bromonaphthalene was obtained at high temperatures.[27] Under the conditions of free-radical bromation, naphthalene undergoes addition.[19]

The fluorination of methyl benzoate at higher fluorine to substrate ratios proceeded by substitution not only in the aromatic nucleus but also in the methyl group of the ester. The fluorine nmr spectrum exhibited, in addition to the signals attributable to the aromatic fluorines, a triplet at ϕ 157 (J_{HF} = 45 cps) and the proton nmr spectrum exhibited a doublet at δ 5.1

(15) Following are several general references on electrophilic aromatic substitution: (a) H. Zollinger, *Experientia*, **12**, 165 (1956); (b) C. C. Price, *Chem. Rev.*, **29**, 37 (1941); H. Gillman, Ed., "Organic Chemistry," 2nd ed, Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1945, p 179 ff; (c) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 221 ff.

(16) M. S. Kharasch and M. G. Berkman, *J. Org. Chem.*, **6**, 810 (1941).

(17) E. Müller, Editor, "Methoden der Organischen Chemie," 4th ed, Vol. 3, Georg Thieme Verlag, Stuttgart, 1962, p 556.

(18) *m*-Dichlorobenzene was obtained in good yield when chlorobenzene was chlorinated in vapor phase at 600°: J. P. Wibaut, L. M. F. Van de Lande, and G. Wallagh, *Rec. Trav. Chim. Pays-Bas*, **56**, 65 (1937). The reaction most likely occurred by the free-radical mechanism.

(19) F. R. Mayo and W. B. Hardy, *J. Amer. Chem. Soc.*, **74**, 911 (1952).

(20) H. E. Fierz-David and F. R. Strähelin, *Helv. Chim. Acta*, **20**, 1458 (1937).

(21) P. S. Varma, K. S. Venkat Raman, and P. M. Nilkautiah, *J. Indian Chem. Soc.*, **21**, 112 (1944).

(22) G. Schiemann and R. Pillarsky, *Chem. Ber.*, **64**, 1340 (1931).

(23) D. H. Derbyshire and W. A. Waters, *J. Chem. Soc.*, 573 (1950).

(24) L. Cenceli, *Chem. Ber.*, **90**, 346 (1957).

(25) A. Laurent, *Ann. Chim.* (Paris), **59**, 216 (1935).

(26) Reference 17, p 669.

(27) F. L. J. Sixma and J. P. Wibaut, *Rec. Trav. Chim. Pays, Bas*, **69**, 577 (1950).

(J_{HF} = 45 cps). These nmr signals were attributed to the fluoromethyl group of the ester on the basis of reported[28] nmr spectra for fluoromethyl trichloroacetate.

The nonaromatic fluorination products obtained in the fluorination of methyl benzoate at high fluorine to substrate ratios were investigated in an attempt to gain some insight into their composition. These glassy solids, possessing molecular weight of *ca.* 600 and empirical structure $C_8H_8F_8O_2$, appear to be trimeric addition products of methyl benzoate containing some residual unsaturation. The fluorine nmr spectra indicated no evidence of aromatic fluorines and only a very broad envelope was exhibited in the region ϕ 160–230. The proton nmr spectra exhibited very broad envelopes at δ 4.3–7.8, and a broad signal at δ 3.6–4.1. The latter was attributed to the superposition of many different signals of the ester methyl group.

In many cases, fluorine nmr spectra of fluorination mixtures exhibited signals in the aromatic region in addition to those of *o*-, *m*-, and *p*-fluoro derivatives, suggesting that aromatic polyfluoro derivatives were produced. Such polysubstituted compounds, however, could not be identified because of a great number of possible isomers. Attempts to increase the relative concentration of polysubstitution products at higher fluorine to substrate ratios resulted in larger amounts of nonaromatic products. For example, the monomeric fraction obtained in the fluorination of bromobenzene using 3 mol of fluorine amounted to only 30% of the total product and contained *o*-, *m*-, and *p*-bromofluorobenzene as the predominant components. The fluorine nmr spectrum also exhibited several other less intense signals in the ϕ 110–140 region attributable to polysubstitution products.

The fluorination of chlorobenzene at a low fluorine to substrate ratio proceeded analogously with that of bromobenzene, yielding a mixture of *o*-, *m*-, and *p*-chlorofluorobenzenes. At a 3:1 fluorine to substrate ratio, on the other hand, only a solid reaction product analyzing for $C_6H_5ClF_4$ was obtained. The physical properties, bp >180° (0.1 mm), mp 127–128°, indicated that this material was a coupling product. The fluorine nmr spectrum exhibited a very broad envelope at ϕ 160–225. The infrared spectrum showed a very broad, intense absorption band at 8–10.5 μ centered at 9.2 μ, three other less pronounced broad absorption bands at 7.2–7.8, 10.7–11.2, and 11.3–12.4 μ, and weak CH absorption peaks at 3.28, 3.43, and 3.51 μ. Except for the CH absorption, the spectrum was very similar to the spectra of perchlorofluoroalkanes. All the above analytical data seem to indicate that the material was a mixture of polychlorofluorocyclohexenes of an approximate composition $(C_6H_5ClF_4)_n$. A great number of possible variations in the composition of individual units of these polycyclohexenes as a result of substitution preceding the addition and condensation, different modes of ring-to-ring junctions, a range of molecular weights, and possibly some residual unsaturation made the characterization of these materials difficult, not only in this specific example, but also in other cases examined. The structures of polycyclic products presented in conjunction with their elemental analyses in the Experimental Section, therefore, should be interpreted as approximations.

Observation made in conjunction with the attempted identification of polysubstitution products seems to indicate that an aromatic substrate and its substitution products are consumed in addition and polymerization reactions at approximately the same rate and that when a certain degree of substitution is reached further fluorination proceeds predominantly by addition. Under exhaustive fluorination conditions all substitution products are eventually consumed in addition reactions.

Acetonitrile was used almost exclusively as the solvent in this work. Although relatively inert toward fluorine, acetonitrile undergoes fluorination to some extent, and on several occasions fluoroacetonitrile was identified in the recovered solvent.[29] In several instances it was also found that polymeric fluorination products of aromatic compounds obtained using acetonitrile as the fluorination medium contained 1–6% of nitrogen, indicating that the solvent was chemically incorporated in the products. It is not clear in what manner acetonitrile entered in these reactions. A similar solvent participation was noticed when carbon tetrachloride or simple aliphatic esters[30] such as methyl acetate or methyl formate was employed. More recently it was found that such side reactions can be eliminated or significantly reduced using perchlorofluoroalkanes, such as 1,1,2-trichloro-1,2,2-trifluoroethane, as the fluorination media. Fluorinations also were carried out using aqueous suspensions of aromatic compounds. Methyl benzoate was fluorinated under these conditions and the distribution of methyl fluorobenzoate isomers was similar to that observed in acetonitrile.

Several general comments regarding the fluorination of aromatic compounds are presented in the form of a summary below.

Direct liquid-phase fluorination of aromatic compounds is a simple procedure and can be performed in the laboratory on a molar scale. The potential dangers of these reactions, however, should not be overlooked. Fluorine is extremely reactive toward organic compounds, and under improper operating conditions direct liquid-phase fluorination reactions might result in serious accidents. In this work, on several occasions, localized flashes of light were observed in the reactor, particularly when undiluted substrates were fluorinated. At fast fluorination rates such firings might become serious. Safety measures recommended in conjunction with direct liquid-phase fluorination reactions are presented in the Experimental Section.

This study was concerned with the feasibility of controllable direct liquid-phase fluorination of aromatic compounds leading to defined products. In conjunction with the previous paper on direct liquid-phase fluorination of halogenated aromatic compounds, it was shown that aromatic compounds undergo fluorination by substitution, and by addition and polymerization, and some insight into the mechanism of fluorination was obtained. On the other hand, many important and

(28) V. Grakauskas, *J. Org. Chem.*, **34**, 963 (1969).

(29) Fluoronitrile was identified by comparing its nmr spectra with those reported for the compound by G. P. Van der Kelen and Z. Eeckhaut, *J. Mol. Spectrosc.*, **10**, 141 (1963).

(30) Aromatic substitution was accomplished employing aliphatic esters as fluorination media, but such solvents are undesirable because they undergo fluorination at a rate comparable with that of aromatic compounds.[28]

interesting aspects of this broad area of research were beyond the scope of the present screening-type study and remain to be investigated.

Experimental Section

General.—The fluorination technique and apparatus were described in the previous paper.[2] Based on our experience with direct liquid-phase fluorination of organic compounds, the following major safety precautions are recommended. The apparatus, particularly the fluorine inlet tubes, must be scrupulously clean and fluorine must be diluted with an inert gas such as helium or nitrogen. We found that it is very convenient to start a fluorination reaction using "lean" fluorine (diluted with nitrogen to 1:6–1:8) and to increase its concentration in the gas mixture as the reaction progresses by reducing nitrogen flow. Reactions should be started slowly and at low temperatures. Both the rate of fluorination and the reaction temperature can be increased later in the run. The reactor should be shielded and all lines containing fluorine under pressure should be located behind a heavy barricade. The latter precaution eliminates a potential danger in the event of rupture of pressure lines. We also found that it is very convenient to incorporate a pressure-calibrated stainless steel cylinder of 500–2000-ml capacity between the fluorine cylinder and the reactor. This auxiliary pressure vessel is charged with fluorine and the main fluorine cylinder is closed. The pressure drop in the auxiliary cylinder during the fluorination indicates the amount of fluorine consumed. An important safety consideration is that the main fluorine cylinder is not directly connected to the apparatus.

Fluorination of Benzene.—A solution of 78 g (1.0 mol) of benzene in 1600 ml of acetonitrile was fluorinated at −35° with 0.7 mol of fluorine. The reaction mixture was diluted with 2500 ml of water, the organic phase was separated, washed with three 500-ml portions of water, dried over anhydrous sodium sulfate, and filtered, and the filtrate was distilled to give 40 g of a colorless liquid, bp 20–30° (25 mm).

Anal. Found: F, 6.3.

The fluorine nmr spectrum exhibited four signals: a multiplet at ϕ 110.8 (*A* 12) assigned to *m*-difluorobenzene, a complex "quintet" at ϕ 113.5 (*A* 1425) assigned to fluorobenzene, a quintet at ϕ 120 (*A* 63) assigned to *p*-difluorobenzene, and a complex multiplet at ϕ 140 (*A* 50) assigned to *o*-difluorobenzene. The reported[13,14] ϕ values are 110.6, 113.5, 120.1, and 139.6, respectively.

The gas chromatographic analysis was obtained using two different columns. The retention times of fluorobenzene and the three difluorobenzene isomers were identical with those of authentic compounds. The relative retention times (benzene = 1.0) on a $^3/_{16}$ in. × 14 ft 10% Carbowax 1000 on Anakrom SD (90/100 mesh) column at 58°, helium flow rate 30 cc/min, were the following: fluorobenzene, 1.24; *m*-difluorobenzene, 1.12; *p*-difluorobenzene, 1.60; and *o*-difluorobenzene, 1.64. Using a $^1/_4$ in. × 12 ft 10% XF-1150 on Anakrom AS (90/100 mesh) column at 46°, helium flow rate 60 cc/min, the relative retention times were the following: *p*-difluorobenzene, 1.17; fluorobenzene, 1.38; *m*-difluorobenzene, 1.50; and *o*-difluorobenzene, 1.68.

In another experiment, a solution of 7.8 g (0.1 mol) of benzene in 350 ml of 1,1,2-trichloro-1,2,2-trifluoroethane was fluorinated at −20° with 0.4 mol of fluorine and the fluorination mixture was distilled to give (a) 1.5 g of a colorless liquid, bp 45–50° (25 mm); (b) 2.p g of viscous liquid, bp 50–60° (0.1 mm); and (c) 9.0 g of distillation residue, bp <90° (0.1 mm), which solidified at room temperature.

Anal. Found: (a) C, 33.4; H, 2.1; F, 63.0; (b) C, 36.0; H, 2.1; F, 63.2; and (c) C, 39.6; H, 2.1; F, 57.5.

Fluorination of Toluene.—Toluene, 63 g (0.685 mol), was fluorinated at −70 to −75° with 0.5 mol of fluorine. The fluorination was slow (5 hr) and several small firings occurred in the reaction flask. The reaction mixture was washed with three 50-ml portions of water, dried over anhydrous sodium sulfate, filtered, and distilled to give 66 g of a colorless liquid, bp 32–36° (25 mm).

Anal. Calcd for C_7H_7F: F, 17.3. Found: F, 6.5.

The fluorine nmr spectrum exhibited three signals: a "quartet" at ϕ 114.9 (*A* 90), a complex multiplet at ϕ 118.4 (*A* 376), and a triplet of triplets at ϕ 119 (*A* 288), assigned to *m*-, *o*- and *p*-fluorotoluene, respectively. The ϕ values reported[14] for *o*-, *m*-, and *p*-toluene are 118.7, 114.6, and 119.2.

The gas chromatographic analysis of the mixture was obtained using a $^3/_{16}$ in. × 14 ft 10% Carbowax 1000 on Anakrom SD (90/100 mesh) column at 58°, helium flow rate 30 cc/min. The relative retention times (toluene = 1.0) of *p*-fluorotoluene (1.16) and *o*-fluorotoluene (1.25) were identical with those of authentic compounds. The signal of *m*-fluorotoluene was superimposed on that of toluene.

Fluorination of Nitrobenzene.—A solution of 24.6 g (0.2 mol) of nitrobenzene in 350 ml of acetonitrile was fluorinated at −15 to −20° with 0.3 mol of fluorine for 2.5 hr. The fluorination mixture was washed with four 400-ml portions of water, dried, and distilled to give 15 g of a pale yellow liquid, bp 45–48° (0.4 mm).

Anal. Calcd for $C_6H_4FNO_2$: C, 51.1; H, 2.81; N, 9.91; F, 13.5. Found: C, 52.4; H, 3.3; N, 10.2; F, 8.0.

The fluorine nmr spectrum exhibited three signals: a triplet of triplets at ϕ 103, a "quartet" at ϕ 110, and a multiplet at ϕ 119, assigned to *p*-, *m*-, and *o*-fluoronitrobenzene, respectively. The reported[14] ϕ values for *o*-, *m*-, and *p*-fluoronitrobenzene are 119.3, 110.4, and 102.9, respectively. The relative ratio of *o*-, *m*-, and *p*-fluoronitrobenzene isomers present in the mixture was 1.5:9:1, respectively. Based on elemental analysis, the reaction mixture contained 35–40% nitrobenzene and 60–65% fluoronitrobenzene.

The distillation residue, a viscous oil amounting to 9.0 g, was not characterized.

Fluorination of Bromobenzene.—A solution of 78.5 g (0.5 mol) of bromobenzene in 650 ml of acetonitrile was fluorinated at −25° with 1.5 mol of fluorine for 3 hr. The reaction mixture was added to 2500 ml of water, the phases were separated, and the organic phase was washed with two 700-ml portions of water. The material, 100 g, was distilled to give 30 g of a pale yellow liquid, bp 50–51° (30 mm).

Anal. Calcd for C_6H_4BrF: C, 41.1; H, 2.3; F, 10.7. Found: C, 40.9; H, 2.4; F, 11.4.

The fluorine nmr spectrum exhibited several signals in the range ϕ 104–140. The two most intense signals, at ϕ 108.6 (*A* 500), a multiplet, and at ϕ 115.8 (*A* 386), a triplet of triplets, were assigned to *o*- and *p*-fluorobromobenzene, respectively. A multiplet at ϕ 111.4 (*A* 170) was assigned to *m*-bromofluorobenzene. The reported values[14] for the above isomers are ϕ 108.2, 116.0 and 111.3, respectively. Less intense signals at ϕ 103.8 (*A* 68), 105.7 (*A* 45), 115 (*A* 48), 117.1 (*A* 80), 131 (*A* 14), 135 (*A* 118), and 140.1 (*A* 78) were unassigned.

The distillation residue, a viscous, pale yellow oil, 68 g, was not further purified.

Anal. Calcd for $(C_6H_5BrF_5)_2$: F, 37.7. Calcd for $(C_6H_5BrF_4)_n$: F, 32.6. Found: F, 34.7.

Fluorination of α,α,α-Trichlorotoluene.—A solution of 58.5 g (0.3 mol) of α,α,α-trichlorotoluene in 650 ml of acetonitrile was fluorinated at −20° with 0.3 mol of fluorine for 1.5 hr. The fluorination mixture was washed with three 1500-ml portions of water and distilled to give 59 g of colorless liquid, bp 48–51° (0.1 mm).

Anal. Calcd for $C_7H_5Cl_3$: C, 43.1; H, 2.6. Calcd for $C_7H_4Cl_3F$: C, 39.3; H, 1.9; F, 8.9. Found: C, 41.4; H, 2.2; F, 4.2.

The fluorine nmr spectrum exhibited three signals: a multiplet at ϕ 104, a triplet of triplets at ϕ 111,[31] and a multiplet at ϕ 112, assigned to *o*-, *p*-, and *m*-fluoro-α,α,α-trichlorotoluene, respectively. The relative ratio of *o*-, *m*-, and *p*-fluoro-α,α,α-trichlorotoluene in the mixture was *ca.* 1:2:1. The concentration of fluoro-α,α,α-trichlorotoluenes in the mixture amounted to *ca.* 50%; the remainder of the material was α,α,α-trichlorotoluene.

Fluorination of Acetophenone.—A solution of 60 g (0.5 mol) of acetophenone in 650 ml of acetonitrile was fluorinated at −20° with 0.5 mol of fluorine for 1.5 hr. The fluorination mixture was washed with four 800-ml portions of water and distilled to give 60 g of a colorless liquid, bp 43–46° (0.2 mm).

Anal. Found: F, 7.1.

The fluorine nmr spectrum exhibited three signals: a triplet of triplets at ϕ 107 ($J_{HF(ortho)}$ = 11.3 cps, $J_{HF(meta)}$ = 7.3 cps) assigned to the *p*-fluoroacetophenone, a multiplet at ϕ 110 assigned to *o*-fluoroacetophenone, and a multiplet at ϕ 112.8 assigned to *m*-fluoroacetophenone. The reported[32,33] ϕ values for *m*- and *p*-fluoroacetophenones are 112.6 and 107.1, respec-

(31) Reported ϕ 111.1.[14]

(32) R. W. Taft, Jr., *J. Phys. Chem.*, **64**, 1805 (1960).

(33) R. W. Taft, Jr., S. Ehrenson, I. C. Lewis, and R. E. Glick, *J. Amer. Chem. Soc.*, **81**, 5352 (1959).

tively. The relative ratio of fluoroacetophenone isomers in the mixture was 1:2:5, for *para*, *ortho*, and *meta* isomers, respectively. The concentration of fluoroacetophenones in the product amounted to *ca.* 50% based on fluorine analysis.

Fluorination of Chlorobenzene.—Chlorobenzene, 84.3 g (0.75 mol), was fluorinated at −35° with 0.45 mol of fluorine for 4.5 hr. The fluorination mixture was washed with three 50-ml portions of water and distilled to give 75 g of a colorless liquid, bp 33–36° (25 mm).

Anal. Calcd for C_6H_4ClF: F, 14.6. Found: F, 10.2.

The fluorine nmr spectrum exhibited three signals: a "quartet" at ϕ 111.3, a multiplet at ϕ 116.2, and a triplet of triplets at ϕ 116.0, assigned to *m*-, *o*-, and *p*-chlorofluorobenzene, respectively. The reported[14] ϕ values for *o*-, *m*-, and *p*-chlorofluorobenzene are 116.4, 111.6, and 116.1. The relative ratio of *o*-, *m*-, and *p*-chlorofluorobenzene isomers was 3:1:9.

The fluorine nmr spectrum of the distillation residue, amounting to 17 g, exhibited a broad envelope at ϕ 160–228.

In another experiment, a solution of 56.3 g (0.5 mol) of chlorobenzene in 500 ml of carbon tetrachloride was fluorinated at −20° with 1.5 mol of fluorine for 4.0 hr. The fluorination mixture was washed with three 200-ml potions of water, dried, and concentrated. The residue, degassed at 180° (0.1 mm), solidified at room temperature, weight 84 g. A sample of this material was recrystallized from cyclohexane to give a white solid, mp 127–129°.

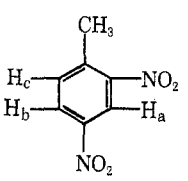
Anal. Calcd for $(C_6H_5ClF_4)_n$: C, 38.2; H, 2.6; F, 40.3; Cl, 18.9. Found: C, 38.3; H, 2.3; F, 37.3; Cl, 21.1.

The fluorine nmr spectrum exhibited a broad envelope at ϕ 160–225.

Fluorination of 2,4-Dinitrotoluene.—A solution of 18.2 g (0.1 mol) of 2,4-dinitrotoluene in 350 ml of acetonitrile was fluorinated at −10° with 0.1 mol of fluorine. The fluorination was sluggish and most of the fluorine escaped from the reactor. The fluorination mixture was diluted with 2000 ml of water and a yellow solid was filtered and washed with three 50-ml portions of water, weight 18.3 g.

The fluorine nmr spectrum exhibited one signal, a doublet (J = 8 cps) of quartets (J = 2 cps) at ϕ 117.5, assigned to the fluorine of 2,4-dinitro-6-fluorotoluene (split into a doublet by the adjacent hydrogen and further split by the CH_3 group into quartets).

The proton nmr spectrum ($CDCl_3$) exhibited four signals attributable to 2,4-dinitrotoluene: a doublet at δ 8.6 (A 90,



$J_{H_a-H_b}$ = 2.5 cps) assigned to the H_a proton; a doublet of doublets at δ 8.4 (A 104, $J_{H_b-H_c}$ = 9 cps, $J_{H_b-H_a}$ = 2.5 cps), assigned to the H_b proton; a doublet at δ 7.6 (A 96, $J_{H_c-H_b}$ = 2.5 cps), assigned to the H_c proton; and a singlet at δ 2.7 (A 332) assigned to the CH_3 protons. A doublet at δ 2.6 (A 15, J_{CH_3-F} = 2.5 cps) was assigned to the CH_3 protons of 2,4-dinitro-6-fluorotoluene. The other two expected signals for the H_a and H_b protons were obscured by the corresponding signals of 2,4-dinitrotoluene. The area ratio of CH_3 signals of the two compounds showed that the concentration of 2,4-dinitro-6-fluorotoluene in the mixture was only 5 mol %.

Fluorination of Methyl Benzoate.—A solution of 68 g (0.5 mol) of methyl benzoate in 650 ml of acetonitrile was fluorinated at −20° with 0.5 mol of fluorine for 2.5 hr. The fluorination mixture was washed with four 750-ml portions of water and distilled to give 58 g of a colorless liquid, bp 32–34° (0.1 mm).

Anal. Calcd for $C_8H_8O_2$: C, 70.6; H, 5.0. Calcd for $C_8H_7FO_2$: C, 62.3; H, 4.6; F, 12.3. Found: C, 68.2; H, 5.8; F, 4.2.

The fluorine nmr spectrum exhibited three signals: a triplet of triplets at ϕ 106.3, a multiplet at ϕ 109.2, and a "quartet" at ϕ 112.3, assigned to methyl *p*-,[34] *o*-, and *m*-fluorobenzoate, respectively. The values obtained for methyl *p*-fluorobenzoate and methyl *o*-fluorobenzoate using authentic samples were ϕ 106.2 and 109.1, respectively. The relative ratio of the three isomers was estimated by integration of the fluorine nmr signals at 1:3:5 for *p*-, *o*-, and *m*-fluorobenzoate, respectively. The distillation residue, amounting to 13 g, bp 100° (0.1 mm), was not characterized.

In another experiment, a solution of 34 g (0.25 mol) of methyl benzoate in 600 ml of carbon tetachloride was fluorinated at −25° with 0.5 mol of fluorine. The fluorination mixture was washed with water and distilled to give 18.5 g of a colorless liquid, bp 33–35° (0.1 mm). The fluorine nmr spectrum showed that *o*-, *m*-, and *p*-fluorobenzoate were present at a 1:5:1 ratio, respectively. A triplet at ϕ 157 (J_{HF} = 45 cps) was assigned to the fluoromethyl benzoate on the basis of the reported fluorine nmr spectrum of fluoromethyl esters.[28] This assignment was confirmed by the proton nmr spectrum, in which a doublet (J_{HF} = 45 cps) was observed at δ 5.1. The distillation residue, amounting to 24.5 g was not further purified.

Anal. Calcd for $(C_8H_5F_3O_2)_n$: C, 49.7; H, 4.2; F, 30.0. Found: C, 48.3; H, 3.9; F, 30.2.

The fluorine nmr spectrum showed no evidence for aromatic fluorines and consisted of a broad envelope at ϕ 160–230. The proton nmr spectrum exhibited broadened superposition of signals in the region δ 4.3–7.8. The methoxy signal was very broad, indicating the presence of many different-CO_2CH_3 groups.

The infrared spectrum exhibited the following absorption peaks: 3.36 (w), 5.8 (s), 6.0 (sh), 6.95 (m), 7.6–8.3 (br envelope, s), and 9.1–9.9 μ (br envelope, s).

In another experiment, a suspension of 34 g (0.25 mol) of methyl benzoate in 700 ml of water was fluorinated at 0–5° with 0.2 mol of fluorine for 2.0 hr. The fluorination mixture was extracted with 80 ml of methylene chloride and distilled to give 15 g of a colorless liquid, bp 36–38° (0.1 mm). The fluorine nmr spectrum showed that *o*-, *m*-, and *p*-fluorobenzoate were present in a 1:3:2 ratio.

The distillation residue, amounting to 19 g, bp >120° (0.1 mm), solidified to a glassy solid at room temperature.

Anal. Found: C, 48.5; H, 4.1; F, 30.1; mol wt, 590 ± 50.

The fluorination of 34 g (0.25 mol) of methyl benzoate in 350 ml of 1,1,2-trichloro-1,2,2-trifluoroethane at −20° with 0.55 mol of fluorine yielded 10 g of a colorless liquid, bp 37–40° (0.1 mm), similar in composition to the monomeric products obtained above. The distillation residue, degassed at 145° (0.1 mm), amounted to 30 g and solidified to a glassy solid at room temperature.

Anal. Found: C, 50.0; H, 3.6; F, 33.0.

Fluorination of Phenetole.—A solution of 24.5 g (0.2 mol) of phenetole in 400 ml of acetonitrile was fluorinated at −30° with 0.2 mol of fluorine. The fluorination mixture was washed with four 500-ml portions of water and distilled to give 23 g of a colorless liquid, bp 28–30° (0.2 mm).

The fluorine nmr spectrum exhibited five signals: a triplet of triplets at ϕ 125 (A 430), a multiplet at ϕ 112.6 (A 90), and a multiplet at ϕ 135.1 (A 1190), assigned to *p*-, *m*-, and *o*-fluorophenetole, respectively. Reported[14] ϕ values are 135.4, 112.4, and 125.2, respectively, for the *ortho*, *meta*, and *para* isomers. Two other signals at ϕ 122 (A 194) and 130 (A 166), both complex multiplets, were unassigned. The signals may represent difluorophenetole isomers.

Fluorination of Naphthalene.—A solution of 12.6 g (0.1 mol) of naphthalene in 850 ml of acetonitrile was fluorinated at −25° with 0.1 mol of fluorine. The fluorination mixture was diluted with 850 ml of water and filtered, and the filter cake was washed with three 50-ml portions of water, wt 13 g. The material was distilled–sublimed at 70–75° (0.1 mm).

The fluorine nmr spectrum exhibited five signals, two of which were too small to quantitate. A "triplet' of doublets at ϕ 115.5 (A 102) was assigned to β-fluoronaphthalene, and a "triplet" at ϕ 123.5 (A 348) was assigned to the α-fluoronaphthalene. A symmetrical triplet at ϕ 130.2 (A 114, J = 7 cps) was unassigned. The reported[35] values for α-fluoronaphthalene and β-fluoronaphthalene are ϕ 123.6 and 115.3, respectively.

In another experiment a solution of 25.6 g (0.2 mol) of naphthalene in 650 ml of acetonitrile was fluorinated at −30° with 2.0 mol of fluorine for 5 hr. The fluorination mixture was washed with four 800-ml portions of water and a viscous oil was degassed at 60° (0.2 mm), wt 65 g.

Anal. Calcd for $(C_{10}H_8F_8)_n$: F, 54.3. Found: F, 53.5.

Registry No.—Benzene, 71-43-2; toluene, 108-88-3; nitrobenzene, 98-95-3; bromobenzene, 108-86-1; α,α,α-

(34) Reported for ethyl *p*-fluorobenzoate, ϕ 107.6.[33]

(35) T. Isobe, K. Inukai, and K. Ito, *J. Chem. Phys.*, **27**, 1215 (1957).

trichlorotoluene, 98-07-7; acetophenone, 98-86-2; chlorobenzene, 108-90-7; 2,4-dinitrotoluene, 121-14-2; methyl benzoate, 93-58-3; phenetole, 103-73-1; naphthalene, 91-20-3.

Acknowledgment.—The author wishes to thank Dr. K. Baum for useful discussions and help with the manuscript, Mr. K. Inouye for elemental analyses, and Mr. L. A. Maucieri for the nmr spectra.

Fluorinated Azo Dyes.[1a] II.[1b] Synthesis and Spectral Properties of 2,6-Difluoro- and 2,3,5,6-Tetrafluoro-4-aminoazobenzene and Their N-Methylated and 4′-Ethyl Derivatives

MOSES J. NAMKUNG, NORMA K. NAIMY, CAROL-ANN COLE, NOBUO ISHIKAWA, AND T. LLOYD FLETCHER

Chemistry Research Laboratory of the Department of Surgery, University of Washington School of Medicine, Seattle, Washington 98105

Received June 23, 1969

A number of new polyfluorinated azo dyes have been synthesized: 2,6-difluoro-4-aminoazobenzene (and its N-methyl and N,N-dimethyl derivatives), 2,3,5,6-tetrafluoro-4-aminoazobenzene (and the N-methyl and N,N-dimethyl derivatives), the 4′-ethyl derivative of all of these dyes, and the 4′-ethyl-substituted derivatives of the 3,5-difluoro azo dyes reported earlier.[1b] Visible and ultraviolet spectra were studied; noteworthy photochromic effects and remarkably slow *cis* to *trans* relaxations are reported. From the spectra of protonated dyes, calculation has been made of the relative amounts of ammonium and azonium forms.

In continuation of our first study,[1b] and for reasons outlined in that paper, we have synthesized the compounds indicated in the above title. Systematic study of the carcinogenicity of various ring-substituted derivatives of 4-dimethylaminoazobenzene (DAB)[2] has led to considerable insight into structure–activity relations. This knowledge has been most significantly built up by Dr. J. A. Miller and Dr. E. C. Miller, McArdle Laboratory, University of Wisconsin, who have summarized much of what is known about many of these compounds.[3] This laboratory is contributing to the knowledge of this area by preparing symmetrically substituted difluoro- and tetrafluoro-AB[2] dyes. We have also synthesized the 4′-ethyl derivatives of these dyes, since this substituent markedly enhances the carcinogenicity (see, *e.g.*, papers by Miller[3] and Sugiura[4] and coworkers) of 4-N-methylaminoazobenzene (MAB)[2] and DAB itself.

In addition, we find that the ultraviolet and visible spectral properties of the new dyes, reported in this paper, are fully as interesting as the properties of the 3,5-difluoro-AB (and N-methyl and -dimethyl derivatives) examined in the earlier work. The marked photochromism[5] (phototropism) and slow *cis* to *trans* isomerization noted for the latter dyes, even in ethanol,[6,7] are still more noteworthy for a number of the dyes in the present series.

Synthesis of this group of intermediates, dyes, and derivatives (Table I) was carried out essentially as described previously,[1b] differences being noted in the Experimental Section. Since nitrosobenzene and 4′-ethylnitrosobenzene condense exclusively in the 4 position of 2,6-difluoro-*p*-phenylenediamine, giving the corresponding 3,5-difluoro-AB,[8] it was necessary to use the 4-N-acetyl derivative of this difluorodiamine[9] to promote condensation to the 2,6-difluoro-AB series (Scheme I). The latter condensations gave poor yields (*ca.* 33%) and were especially sluggish, increased temperature having no effect on this lethargy.

4-Ethylnitrosobenzene, whose properties have not been recorded before,[10] is less stable than nitrosobenzene or 4-methylnitrosobenzene. Since there is considerable decomposition upon steam distillation, the compound must instead be extracted from the reaction mixture and distilled under vacuum.

Synthesis of the tetrafluoro dyes was effected in a manner similar to that for the 2,6-difluoro series (Scheme I), except that the initial condensation took place between the nitroso compound and tetrafluoro-*p*-phenylenediamine. These were also slow reactions (7 days for maximum yields of 46–48%).

Attempts to formylate the 2,3,5,6-tetrafluoro-AB dyes failed; therefore, this route to the corresponding MAB dyes was impossible. We succeeded in methylating N-acetyl-2,3,5,6-tetrafluoro-AB, however, with subsequent hydrolysis of the acetyl group to give 2,3,5,6-tetrafluoro-MAB in very low overall yield. Acetylation of 4′-ethyl-2,3,5,6-tetrafluoro-AB gave only 44% N-acetyl dye. Attempted methylation of the latter and hydrolysis gave no N-monomethylated dye. Instead we recovered only a small amount of a ring-ethoxylated product.

(1) (a) Supported in part by Grant CA-01744 from the National Cancer Institute and by Career Development Award 5-KO3-CA-14,991 (T. L. F.). (b) Part I: N. Ishikawa, M. J. Namkung, and T. L. Fletcher, *J. Org. Chem.*, **30**, 3878 (1965).

(2) The following abbreviations are used in this paper: AB, 4-aminoazobenzene, MAB, 4-N-methylaminoazobenzene; DAB, 4-N,N-dimethylaminoazobenzene.

(3) J. A. Miller, E. C. Miller, and G. C. Finger, *Cancer Res.*, **17**, 387 (1957).

(4) K. Sugiura, M. L. Crossley, and C. J. Kensler, *J. Nat. Cancer Inst.*, **15**, 67 (1954).

(5) See R. Lovrien and J. C. B. Waddington, *J. Amer. Chem. Soc.*, **86**, 2315 (1964), footnote 2.

(6) W. R. Brode, J. H. Gould, and G. W. Wyman, *ibid.*, **75**, 1856 (1953).

(7) M. N. Inscoe, J. H. Gould, and W. R. Brode, *ibid.*, **81**, 5634 (1959).

(8) The structure of 4′-ethyl-3,5-difluoro-AB was confirmed by deamination and unambiguous synthesis of the deaminated product by condensation of 4-ethylnitrosobenzene and 3,5-difluoroaniline (method A).

(9) We reported[1b] synthesis of this compound by reductive splitting of the azo group with 85% hydrazine hydrate and palladium on carbon, noting that this method appears to be new, but we later discovered that this type of reduction was reported earlier by S. Pietra, *Ann. Chim.* (Rome), **47**, 410 (1957).

(10) This compound was reported (a) by R. E. Lutz and M. R. Lytton [*J. Org. Chem.*, **2**, 73 (1937)], mp 22°, but described as impure; and (b) by this laboratory [M. E. Taylor and T. L. Fletcher, *J. Amer. Chem. Soc.*, **80**, 2246 (1958)], without physical constants or analyses. We now suspect that the compound was impure in our earlier preparation, because its use then resulted in an anomalous product. It had been steam distilled, and we now find that the compound is readily oxidized during this operation.