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Electrochemical Fluorination of Benzamide and Acetanilide in Anhydrous HF and in Acetonitrile

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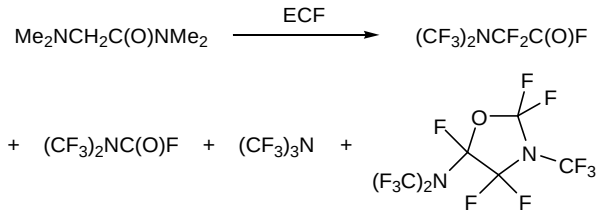
Abstract—Electrochemical fluorination of benzamide in anhydrous hydrogen fluoride does not involve the amide group but occurs exclusively at the aromatic ring, yielding isomeric fluoro- and difluorobenzamides and 3,3,6,6-tetrafluoro-1,4-cyclohexadienecarboxamide. Electrochemical fluorination of benzamide in acetonitrile as solvent gives the same products, as well as benzonitrile and its fluorinated derivatives and products of hydrolysis and fluorination of acetonitrile. Electrochemical fluorination of acetanilide in anhydrous HF leads to complete tarring of the reaction mixture, while its fluorination in acetonitrile results in selective formation of *m*-fluoroacetanilide.

Fluorination of aromatic compounds with various fluorinating agents under various conditions has long attracted researchers' attention from the viewpoint of synthesis of fluoroaromatic products. Direct fluorination of various aromatic compounds with elemental fluorine [1] and their oxidative fluorination with higher metal fluorides (AgF_2, CoF_3, etc.) [2] were reported. We previously studies electrochemical fluorination of some functionalized fatty–aromatic compounds of the general formula $PhXCH_3$ (X = SO_2 [3], CO [4]) and showed that the process occurs exclusively at the aromatic ring, the methyl group remaining intact. In continuation of our studies in this field [3–5], in the present work we examined electrochemical fluorination of benzamide (**I**) and acetanilide (**II**) in anhydrous hydrogen fluoride and in acetonitrile with the goal of extending the series of substrates to compounds having other functional groups.

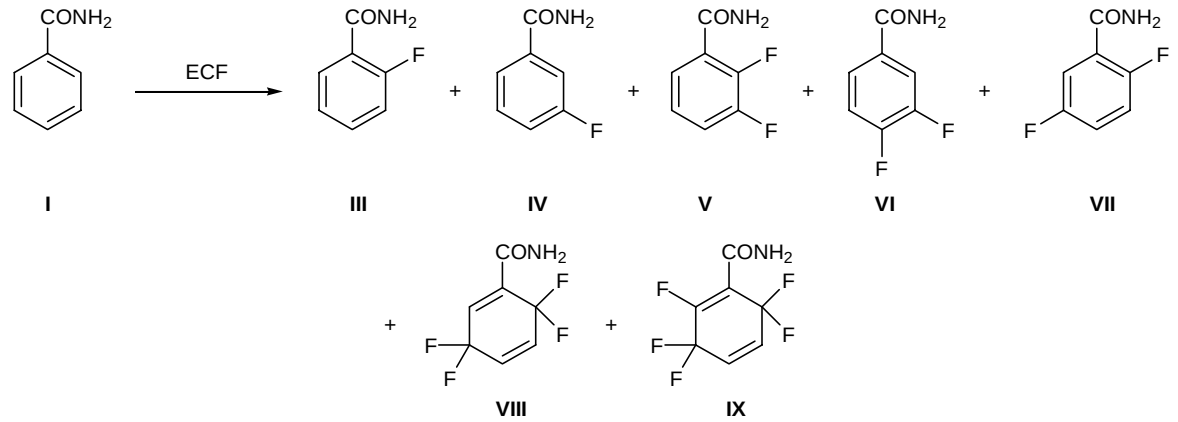
Electrochemical fluorination (ECF) of the simplest amides, such as formamide, acetamide [6, 7], and also urea and *N*,*N*-dimethylurea [8], leads to profound decomposition of the substrates with formation of gaseous products: N_2, N_2O, CO_2, NF_3, CF_4, COF_2, CHF_3, C_2F_6 (the two latter were obtained only from acetamide and *N*,*N*-dimethylurea). Electrochemical fluorination of aliphatic carboxamides gives products of complete fluorination of the alkyl groups and transformation of the amide group into fluorocarbonyl moiety. Also, α-cleavage and cyclization products are formed in small amounts as shown in Scheme 1 with *N*,*N*,*N'*,*N'*-tetramethylglycine amide as an example [9]. We have found no published data on electrochemical fluorination of aromatic amides or their derivatives.

Scheme 1.



The product mixtures obtained by electrochemical fluorination of benzamide (**I**) and acetanilide (**II**) were analized by gas chromatography–mass spectrometry (GC–MS). As with methyl phenyl sulfone [3] and acetophenone [4], the fluorination of benzamide in anhydrous hydrogen fluoride occurred exclusively at the aromatic ring while the carboxamide group remained unchanged. The major fluorination products were *o*- and *m*- fluorobenzamides **III** and **IV**, 2,3-, 3,4-, and 2,5-difluorobenzamides **V**–**VII,** and 3,3,6,6-tetrafluoro-1,4-cyclohexadienecarboxamide (**VIII**); also, traces of pentafluoro-1,4-cyclohexadienecarboxamide (**IX**) were detected (Scheme 2). The products were separated by column chromatography on silica gel or preparative gas–liquid chromatography, and

Scheme 2.



their structure was unambiguously proved by ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy, as well as by comparison with published data for known compounds (see Experimental). According to the ^{19}F NMR spectra, the molar ratio **III**:**IV**:**V**:**VI**:**VII**:**VIII** was 8:16:10:6:27:33.

A considerably different pattern was observed in the electrochemical fluorination of benzamide in acetonitrile solution. GC–MS analysis of the reaction mixture (after distillation) showed the presence of the following compounds (in the order of increase in the retention time; the relative peak intensities are given in parentheses): FC_6H_4CN (3), PhCN (56), FC_6H_4CN (7), **VIII** (11), $F_2C_6H_3CONH_2$ (6), $FC_6H_4CONH_2$ (9), $PhCONH_2$ (8).

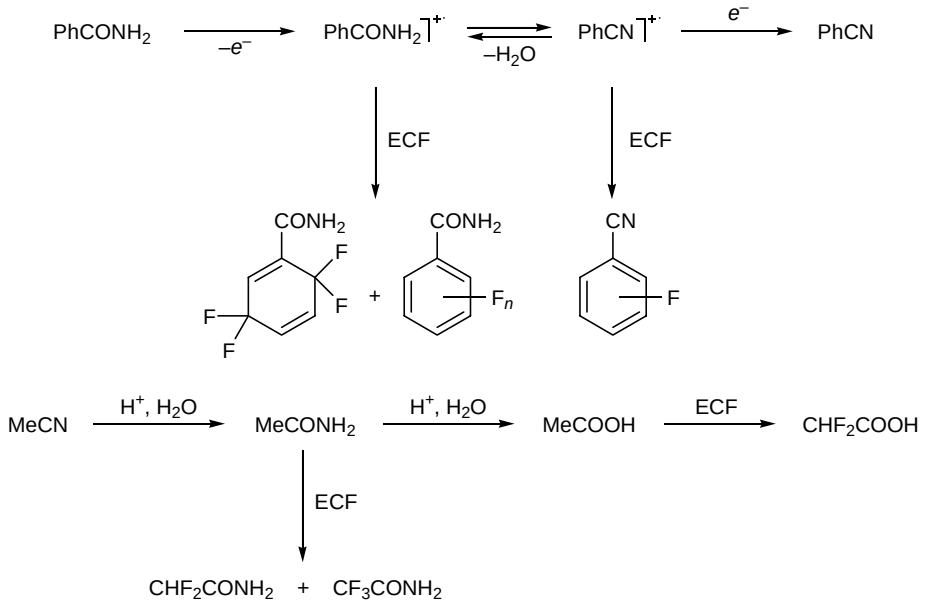
The structure of the resulting fluorobenzonitrile isomers can be presumed on the basis of their relative retention time with respect to benzonitrile. Taking into account that a more polar compound should be characterized by a lower retention time in a nonpolar column, the isomer leaving the column first (minor) is likely to be *o*-fluorobenzonitrile (which is more polar than benzonitrile); the second isomer whose retention time is slightly greater than that of benzonitrile, is *m*-fluorobenzonitrile. The calculated [HF/6-31G(*d*,*p*)] dipole moments of benzonitrile and its *o*-, *m*-, and *p*-fluoro derivatives are, respectively 4.85, 5.69, 4.15, and 3.23 D, in keeping with the above assignment.

Apart from the benzamide transformation products, those resulting from hydrolysis and fluorination of acetonitrile were formed: CH_3CO_2H, CF_3CONH_2, CH_2FCONH_2, CH_3CONH_2, and CHF_2CO_2H. Difluoroacetic acid was identified by NMR spectroscopy. In the ^{13}C NMR spectrum we observed signals at δ_C 106.83 (t, $^{1}J_{CF}$ = 247.8 Hz) and 165.48 ppm (t, $^{2}J_{CF}$ = 28.2 Hz), and a doublet at δ_F –127.27 ppm ($^{2}J_{HF}$ = 53.6 Hz) was present in the ^{19}F NMR spectrum. Difluoroacetic acid was the major product: the doublet at δ_F –127.27 ppm was the most intense in the ^{19}F NMR spectrum of the product mixture.

Thus the major product of electrochemical fluorination of benzamide in acetonitrile is benzonitrile, and the process is accompanied by transformation of the solvent into acetamide and further reactions of the latter. Formalistically, the process can be regarded as functional group exchange between the amide and nitrile. This result is very surprising, for no such reactions are known in synthetic organic chemistry. Taking into account that the electrochemical fluorination was carried out in anhydrous medium (which was subjected to preliminary electrolytic treatment to remove traces of water), the following scheme of transformations seems to be probable. Oxidation of the substrate at an anode gives benzamide radical cation which reacts further along two pathways. The first of these is electrochemical fluorination leading to fluoro-substituted benzamides and tetrafluorocyclohexadienecarboxamide **VIII**, and the second is reversible dehydration with formation of benzonitrile radical cation. Electrochemical fluorination of the latter yields isomeric fluorobenzonitriles, while its reduction at a cathode affords benzonitrile. In acid medium, the solvent (acetonitrile) is hydrolyzed with water liberated upon dehydration of benzamide. As a result, acetamide and acetic acid are formed, and they are then converted into the respective electrochemical fluorination products (Scheme 3).

The key stage in the proposed scheme is dehydration of benzamide. Here, it remains unclear why dehydration of benzamide (which usually requires heating in the presence of dehydrating agents, such as P_2O_5, PCl_5, etc.) readily occurs under conditions of

Scheme 3.



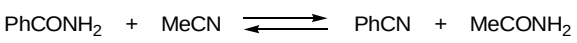
electrochemical fluorination in acetonitrile and why no benzonitrile is formed in the absence of a solvent. To answer the above questions, we performed HF/6-31G (*d*,*p*) quantum-chemical calculations of the molecules and radical cations involved in the process. The results showed that the dehydration of benzamide/hydration of acetonitrile (Scheme 4) is a weakly endothermic reaction (ΔH = 4.2 kJ/mol). On the other hand, an analogous process with participation of the corresponding radical cations (which are generated by electrochemical oxidation; Scheme 5) is exothermic (ΔH = –28.9 kJ/mol). These result allow us to understand the observed transformations on a qualitative level. The absence of benzonitrile among the products of electrochemical fluorination without a solvent capable of undergoing hydration is explained as follows. As might be expected, the process of benzamide dehydration *per se* is strongly endothermic (ΔH = 90.8 kJ/mol for benzamide and ΔH = 415.5 kJ/mol for the corresponding radical cation $[PhCONH_2]^{+\cdot}$).

We observed no transformation of the cyano group in benzonitrile into trifluoromethyl, though Yonekura *et al*. [10] reported on electrochemical fluorination of isomeric trifluoromethyl-substituted benzonitriles with formation of 10–20% of perfluoro(dimethylcyclohexanes).

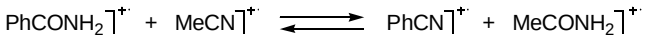
The possibility of using acetonitrile as solvent in electrochemical fluorination of aromatic compounds is determined by the fact that its anode oxidation potential is higher than those of the substrates [11]. However, it should be taken into account that at high potentials in the absence of more readily oxidizable substrates acetonitrile is also capable of undergoing fluorination to give gaseous products: CF_3CN, $C_2F_5NF_2$, C_2F_6, and NF_3 [12].

We also examined electrochemical fluorination of acetanilide with a view to compare the effects of amide groups attached to benzene ring through the carbon [$PhC(O)NH_2$] and nitrogen atoms [$MeC(O)NHPh$]. The reaction in anhydrous hydrogen fluoride was accompanied by almost complete tarring, so that we failed to isolate and identify any individual product. By contrast, the fluorination of acetanilide in acetonitrile was highly selective, and *m*-fluoroacetanilide (**X**) was formed almost exclusively. The substrate

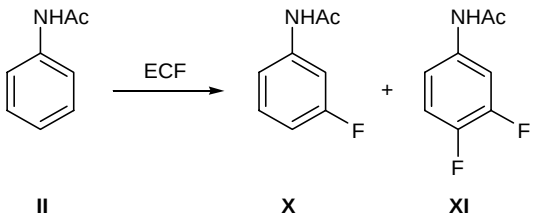
Scheme 4.



Scheme 5.



Scheme 6.



conversion in 18 h (current 1.1 A) was 40%. GC–MS analysis of the reaction mixture revealed traces of a difluoro derivative [presumably, *N*-(3,4-difluorophenyl)acetamide (**XI**)], products of hydrolysis of acetonitrile (acetamide, acetic acid), and fluorination products of the latter (Scheme 6). No oxidative fluorination product, *N*-(3,3,6,6-tetrafluoro-1,4-cyclohexadienyl)acetamide, was detected.

EXPERIMENTAL

The ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker DPX-400 spectrometer at 400, 100, and 376 MHz, respectively; $CDCl_3$ was used as solvent, and HMDS, as internal reference (for ^{1}H and ^{13}C); the chemical shifts are given relative to TMS (^{1}H, ^{13}C) and CCl_3F (^{19}F). GC–MS analysis was performed on a Hewlett–Packard HP 5971A mass-selective detector (70 eV) coupled with an HP 5890 gas chromatograph; Ultra-2 column (5% of phenylmethylsilicone), injector temperature 250°C, oven temperature programming from 70 to 280°C at 20 deg/min. GLC analysis was performed on an LKhM-8MD chromatograph using 2000×3-mm columns packed with 15% of polyphenylmethylsiloxane on Chromaton N-AW; thermal conductivity detector; carrier gas helium. A PAKhV-07 instrument was used for preparative gas–liquid chromatography; column 5000×8 mm, stationary phase 5% of XE-60 on Chromaton N-AW DMCS.

Electrochemical fluorination was carried out in a 130-cm^3 stainless steel electrolyzer equipped with nickel electrodes (overall surface area 63 cm^2), valves for supplying hydrogen fluoride and product discharge, and a reflux condenser filled with a 1:1 acetone–diethyl ether mixture which was cooled to –30°C using liquid nitrogen.

Electrochemical fluorination of benzamide. *a.* A cooled electrolytic cell was charged with 120 g of anhydrous hydrogen fluoride and 5.1 g of benzamide. The electrolysis was carried out over a period of 19 h (21 A h; anode current density 1.75 A/dm^2, voltage 6.5–7.0 V, temperature ~5°C. When the reaction was complete, the cell was discharged into an evaporator, excess hydrogen fluoride was removed, the residue was diluted with diethyl ether, NaF was added to bind residual HF until neutral pH, the solution was dried over $MgSO_4$, and the solvent was distilled off. The resulting mixture containing unreacted benzamide and fluorination products (4.8 g) was separated into fractions by preparative GLC, and each fraction was then subjected to column chromatography on silica gel using gradient elution with hexane–diethyl ether (3:2), diethyl ether, diethyl ether–methanol (16:1), and methanol. We thus isolated pure product **VIII** and fractions enriched in mono- or difluorinated products. These fractions were analyzed by ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy and by gas chromatography–mass spectrometry.

b. A cooled electrolytic cell was charged with 100 g of anhydrous hydrogen fluoride, 10 g of benzamide, and 30 ml of anhydrous acetonitrile. The electrolysis was performed at an anode current density of 1.75 A/dm^2; voltage 6.0–6.8 V; temperature ~5°C. After 35 h (39 A h), the conversion was 68%. The cell was discharged into an evaporator, excess hydrogen fluoride was removed, the residue was diluted with diethyl ether, NaF was added to bind residual HF until neutral pH, the solution was dried over $MgSO_4$, the solvent was distilled off, and the residue was subjected to fractional distillation under reduced pressure. Fractions boiling below 60°C and in the temperature range 60–100°C (1 mm) were collected and analyzed by ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy and by GC–MS.

3-Fluorobenzamide (IV). ^{1}H NMR spectrum: δ 6.1–7.5 ppm, m. ^{13}C NMR spectrum, δ_C, ppm: 114.36 d (C^2, $^{2}J_{CF}$ = 22.8 Hz), 118.50 d (C^4, $^{2}J_{CF}$ = 20.7 Hz), 122.87 s (C^6), 129.90 d (C^5, $^{3}J_{CF}$ = 7.3 Hz), 135.29 s (C^1), 162.25 d (C^3, $^{1}J_{CF}$ = 247.4 Hz), 170.80 s ($CONH_2$); published data [13] (DMSO-d_6), δ_C, ppm: 114.52, 119.04, 123.87, 130.88, 134.27, 161.83, and 164.51 for C^2, C^4, C^6, C^5, C^1, C^3, and $CONH_2$, respectively. ^{19}F NMR spectrum: δ_F –112.13 ppm. Mass spectrum, *m*/*z*, (I_{rel}, %): 139 (62) $[M]^+$, 123 (100) $[M-NH_2]^+$, 95 (52) $[M-CONH_2]^+$, 75 (25) $[95-HF]^+$, 44 (28) $[CONH_2]^+$.

2,5-Difluorobenzamide (VII). ^{1}H NMR spectrum: δ 6.1–7.5 ppm, m. ^{13}C NMR spectrum, δ_C, ppm: 117.46 d.d (C^3, $^{2}J_{CF}$ = 28.4, $^{3}J_{CF}$ = 5.2 Hz), 120.27 d.d (C^4, $^{2}J_{CF}$ = 22.8, $^{3}J_{CF}$ = 7.3 Hz), 121.82 (C^1), 124.43 d (C^6, $^{2}J_{CF}$ = 20.3 Hz), 156.62 d (C^2, $^{1}J_{CF}$ = 244.8 Hz), 158.49 d (C^5, $^{1}J_{CF}$ = 244.0 Hz), 164.52 ($CONH_2$). ^{19}F NMR spectrum, δ_F, ppm: –117.38 (2-F), –118.71 (5-F). Mass spectrum, *m*/*z*, (I_{rel}, %): 157 (76) $[M]^+$, 141 (100) $[M-NH_2]^+$, 113 (50) $[M-CONH_2]^+$, 63 (23) $[C_5H_3]^+$, 44 (34) $[CONH_2]^+$.

3,3,6,6-Tetrafluoro-1,4-cyclohexadienecarboxamide (VIII). mp 84–85°C. ^{1}H NMR spectrum, δ, ppm: 6.28 d.t (5-H, $^{3}J_{HH}$ = 10.3, $^{3}J_{HF}$ = 5.3 Hz), 6.34 d.d (2-H, $^{4}J_{HH}$ = 2.6, $^{3}J_{HF}$ = 4.2 Hz), 6.35 d.d.t (4-H, $^{3}J_{HH}$ = 10.3, $^{3}J_{HF}$ = 4.2, $^{4}J_{HH}$ = 2.6 Hz), 7.17 m (2H, NH_2). ^{13}C NMR spectrum, δ_C, ppm: 109.79 t.d

(C^6, J_{CF} = 227.4, J_{CH} = 9.8 Hz), 110.62 t.d (C^3, J_{CF} = 228.5, J_{CH} = 9.6 Hz), 128.84 d.t.t (C^5, J_{CH} = 173.6, $^2J_{CF}$ = 31.3, $^3J_{CF}$ = 9.1 Hz), 129.15 d.t.t (C^4, J_{CH} = 173.8, $^2J_{CF}$ = 30.5, $^3J_{CF}$ = 9.4 Hz), 134.81 d.t.t (C^2, J_{CH} = 173.6, $^2J_{CF}$ = 31.6, $^3J_{CF}$ = 6.7 Hz), 133.59 t.t (C^1, $^2J_{CF}$ = 27.5, $^3J_{CF}$ = 9.0 Hz), 161.91 ($CONH_2$). ^{19}F NMR spectrum, δ_F, ppm: –95.59 m (3-F), –95.26 m (5-F). Mass spectrum, *m*/*z* (I_{rel}, %): 195 (67) $[M]^+$, 179 (18) $[M - NH_2]^+$, 159 (45) $[179 - HF]^+$, 151 (18) $[M - CONH_2]^+$, 132 (70) $[C_6H_3F_3]^+$, 113 (10) $[C_6H_3F_2]^+$, 101 (34) $[C_5H_3F_2]^+$, 81 (13) $[C_5H_2F]^+$, 75 (18) $[C_3HF_2]^+$, 63 (21) $[C_5H_3]^+$, 44 (100) $[CONH_2]^+$. Found, %: C 43.20; H 2.82; F 39.58; N 7.08. $C_7H_5F_4NO$. Calculated, %: C 43.09; H 2.58; F 38.95; N 7.18.

Pentafluoro-1,4-cyclohexadienecarboxamide (IX). Mass spectrum, *m*/*z* (I_{rel}, %): 213 (43), $[M]^+$, 197 (11) $[M - NH_2]^+$, 177 (9), $[M - HF]^+$, 169 (28) $[M - CONH_2]^+$, 150 (33) $[169 - F]^+$, 119 (55) $[C_5H_2F_3]^+$, 81 (20) $[C_5H_2F]^+$, 75 (13) $[C_3HF_2]^+$, 44 (100) $[CONH_2]^+$.

Electrochemical fluorination of acetanilide (**II**) in acetonitrile was performed as described above using 100 ml of hydrogen fluoride, 10 g of acetanilide, and 30 ml of acetonitrile; time 18 h (20 A h), voltage 6.0–6.5 V, current density 1.75 A/dm^2). The substrate conversion was ~40%. After appropriate treatment, the reaction mixture was distilled at 80–110°C (1 mm) and analyzed by NMR and GC–MS.

3-Fluoroacetanilide (X). Mass spectrum, *m*/*z* (I_{rel}, %): 153 (15) $[M]^+$, 111 (100) $[M - CH_2CO]^+$, 43 (28) $[COCH_3]^+$.

Quantum-chemical calculations were performed with the aid of Gaussian 98 software [14] which was kindly provided by V.A. Lopyrev. The authors are grateful to N.A. Kalinina for performing product separation by preparative gas–liquid chromatography.

REFERENCES

1. Grakauskas, V., *J. Org. Chem.*, 1970, vol. 35, p. 723.
2. Feiring, A.E., *J. Org. Chem.*, 1979, vol. 44, p. 1252.
3. Shainyan, B.A., Danilevich, Yu.S., Bel'skii, V.K., Stash, A.I., Grigor'eva, A.A., and Chuvashev, Yu.A., *Russ. J. Org. Chem.*, 2002, vol. 38, p. 1462.
4. Shainyan, B.A., Danilevich, Yu.S., Grigor'eva, A.A., and Chuvashev, Yu.A., *Russ. J. Org. Chem.*, 2003, vol. 39, p. 1581.
5. Grigor'eva, A.A., Shainyan, B.A., Kaurova, G.I., Gracheva, E.I., Lesnevskaya, N.B., and Barabanov, V.G., *Zh. Prikl. Khim.*, 2002, vol. 75, p. 1112.
6. Tasaka, A., Sakaguchi, H., and Aki, R., *J. Fluorine Chem.*, 1982, vol. 21, p. 51.
7. Tasaka, A., Sakaguchi, H., Aki, R., Ihara, H., Saka, K., and Yamamoto, T., *J. Fluorine Chem.*, 1985, vol. 27, p. 23.
8. Chang, B., Watanabe, N., and Nakanishi, K., *Electrochim. Acta*, 1972, vol. 17, p. 1317.
9. Young, A.G. and Dresdner, R.D., *J. Am. Chem. Soc.*, 1958, vol. 80, p. 1889.
10. Yonekura, M., Nagase, S., Baba, H., Kodaira, K., and Takashi, A., *Bull. Chem. Soc. Jpn.*, 1976, vol. 49, p. 1113.
11. Rozhkov, I.N., Bukhtiarov, A.V., and Knunyants, I.L., *Izv. Akad. Nauk SSSR. Ser. Khim.*, 1972, p. 1130.
12. Haruta, M. and Watanabe, N., *J. Fluorine Chem.*, 1976, vol. 7, p. 159.
13. De Rosa, M., Brown, K., McCoy, M., Ong, K., and Sanford, K., *J. Chem. Soc., Perkin Trans. 2*, 1993, p. 1787.
14. Frisch, M.J., Trucks, G.W., Schlegel, H.B., Scuseria, G.E., Robb, M.A., Cheeseman, J.R., Zakrzewski, V.G., Montgomery, J.A., Jr., Stratmann, R.E., Burant, J.C., Dapprich, S., Millam, J.M., Daniels, A.D., Kudin, K.N., Strain, M.C., Farkas, O., Tomasi, J., Barone, V., Cossi, M., Cammi, R., Mennucci, B., Pomelli, C., Adamo, C., Clifford, S., Ochterski, J., Petersson, G.A., Ayala, P.Y., Cui, Q., Morokuma, K., Malick, D.K., Rabuck, A.D., Raghavachari, K., Foresman, J.B., Cioslowski, J., Ortiz, J.V., Stefanov, B.B., Liu, G., Liashenko, A., Piskorz, P., Komaromi, I., Gomperts, R., Martin, R.L., Fox, D.J., Keith, T., Al–Laham, M.A., Peng, C.Y., Nanayakkara, A., Gonzalez, C., Challacombe, M., Gill, P.M.W., Johnson, B., Chen, W., Wong, M.W., Andres, J.L., Gonzalez, C., Head–Gordon, M., Replogle, E.S., and Pople, J.A., *Gaussian 98. Revision A.6*, Pittsburgh: Gaussian, 1998.