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NUCLEOPHILIC AROMATIC SUBSTITUTION; KINETICS OF FLUORINE-18 SUBSTITUTION REACTIONS IN POLYFLUOROBENZENES. ISOTOPIC EXCHANGE BETWEEN $^{18}F^-$ AND POLYFLUOROBENZENES IN DIMETHYLSULFOXIDE. A KINETIC STUDY

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SUMMARY

Nucleophilic aromatic substitution reactions of C_6F_6, C_6XF_5 (X = H, Cl, Br), $C_6H_2F_4$, o-$C_6H_4FNO_2$ and p-$C_6H_4FNO_2$ by the fluoride anion were studied in DMSO utilizing fluorine-18. Substitution of fluorine by fluorine-18 is the only reaction observed with a C_6F_6 substrate. With other substrates fluorine substitution is predominant. The kinetic studies provide results consistent with a S_NAr two step mechanism and suggest an intermediate analogous to that for electrophilic aromatic substitution. Consideration of σ^- indicates consistency with methoxide ion substitution results with similar substrates. The possible utility of these reactions in labeling aromatic compounds is noted.

INTRODUCTION

Nucleophilic displacement of fluorine from highly fluorinated aromatic substrates has been the subject of extensive investigation, [1] utilizing a wide range of nucleophiles. A conspicuous exception does exist, concerning one of the most simple nucleophilic attacks, that of fluoride ion

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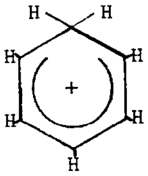
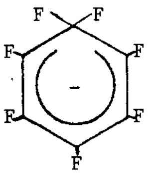
itself on polyfluorobenzenes. Research in this area has been hampered by a lack of synthetic interest, by the anticipated lack of reactivity of the fluoride anion toward aryl centers, unless very highly activated, [2] and especially by the considerable experimental difficulties, associated with the limited availability and the relatively short (109 minutes) half life of ^{18}F, the longest-lived isotope of fluorine.

In the past few years however the picture has largely changed, owing to recent interest in the synthesis of ^{18}F-labeled radiopharmaceuticals, and their growing applications [3]. This has led to experimental advances in the methods of preparation, purification, and assay of ^{18}F-labeled compounds.

The study of the F^- attack on highly fluorinated aromatics is a subject of considerable mechanistic interest in its own right since it may represent a significant extension of the classical framework of aromatic substitution. As an example, one can consider the analogous symmetric properties of the most simple intermediate of electrophilic substitution, the Wheland adduct (I), and the anionic adduct (II), expected [4] to be



(I)



(II)

involved in the nucleophilic attack of the fluoride ion on hexafluorobenzene. These considerations have been the focus of the extensive theoretical work in closely related aliphatic substitution reactions [5]. Thus experimental information concerning (II) can prove of considerable value from the mechanistic and theoretical standpoint. In fact, the reaction of the fluoride ion with hexafluorobenzene appears to provide a suitable model on which to base a mechanistic and kinetic study of nucleophilic aromatic substitution involving activated halogenobenzenes. In addition, the study of the fluoride ion reactivity toward 'substituted' hexafluorobenzenes, e.g. C_6XF_5 substrates, can provide mechanistic information on nucleophilic aromatic substitution, in much the same way as the analysis of the effects of substituents has played a vital role in the development of the current theories of electrophilic aromatic substitution.

Finally, the experimental determination of the kinetic and mechanistic features of the reaction of $^{18}F^-$ with activated halogenated arenes can be of practical interest, as a possible route from the most simple and readily available reagent, ^{18}F-fluoride ion, to ^{18}F-labeled aromatic precursors for the synthesis of radiopharmaceuticals and metabolic tracers.

As model systems we have investigated the isotopic exchange between $^{18}F^-$ and selected polyfluorinated benzenes, e.g. C_6F_6, C_6XF_5 (X = H, Cl, Br) and $C_6X_2F_4$ (X = H). Dimethylsulfoxide (DMSO) was chosen as the solvent. In addition to its recognized role in nucleophilic substitution reactions, [6] other favorable properties include the ability to dissolve relatively large amounts of inorganic halides, [7] its high boiling point, and its acceptable thermal stability [8].

EXPERIMENTAL

Materials

Anhydrous KF and RbCl were obtained from Alfa Products Division of Ventron, Inc. and further dehydrated at 150°C under high vacuum. Research grade C_6F_6, C_6BrF_5 and C_6ClF_5 were purchased from Aldrich Chemical Co. Inc., while C_6HF_5 and the three $C_6H_2F_4$ isomers were obtained from Peninsular Chemresearch, Inc.

The purity of the substrates was checked by glpc and hplc. When required, e.g. in the case of the $C_6H_2F_4$ isomers, the substrates were purified by preparative glc, using a 4.57 meter, 6.5 mm o.d., 4.5 mm i.d. dimethylsulfolane column operated at 45°C, with a He flow rate of 90 ml min^{-1}.

DMSO Solvent

DMSO, obtained from Matheson, Coleman and Bell Co., was dried for one month over 4 Å Molecular Sieve (Fischer Scientific Co.) which had been activated at 350° under vacuum. Preliminary tests showed that the rate of ^{18}F-exchange with C_6F_6 at 60°C was subject to erratic fluctuations when the dried DMSO sample, containing ca. 20 ppm water, according to a Karl Fischer titration [9], was used as the solvent. This erratic behavior was traced to the minute and variable amounts of water introduced into the reaction medium by the ^{18}F-labeled fluoride. Preparation of this reagent, involving several steps carried out with remotely controlled and heavily shielded equipment, did not allow removal of the water to a degree comparable with the residual water content of the dried DMSO. In order to overcome this difficulty, a carefully controlled amount of water was introduced into the DMSO, bringing its total water content up to 85 ± 7 ppm, as measured by Karl Fischer titration. Apparently, such an amount of water was considerably larger than that introduced by the radiochemical manipulations prior to preparation of the 'exchange solution' The rate of $^{18}F^-$ exchange with polyfluorobenzenes was consistent and reproducible when the controlled water concentration DMSO was used as a solvent.

Preparation of the Exchange Solution

In order to prepare $^{18}F^-$ ion under controlled conditions, i.e. with very low but known amounts of H_2O present in the solution, it was decided not to use the conventional H_2O targets and ^3He bombardment to produce fluorine-18. Instead $^{18}F-F_2$ was prepared from a Ne - 0.1% F_2 target using the $^{20}Ne(d,\alpha)^{18}F$ reactions [10]. Advantage was taken of a technique [11] previously exploited for the quantitative glpc analysis of F_2/O_2 mixtures involving heterogeneous exchange between $^{18}F-F_2$ on rubidium chloride yielding microscopic amounts of ^{18}F rubidium-fluoride on the surface of the rubidium chloride. The $^{18}F-F_2$ Ne gas mixture was passed through a pyrex capillary 10 cm ℓ x 1 mm i.d. containing finely ground RbCl. The capillary was mounted in a 7 mm x 27 cm ionization chamber (Capintec, model CRC4534) so that build-up of ^{18}F activity could be followed. The capillary was flushed with a stream of dry research grade neon and the contents transferred to a pyrex flask fitted with the appropriate gas inlet and transfer tubes. The solid RbCl-^{18}F-Rb^{18}F mass was slurried with dry DMSO containing additional fluoride ion (as KF) as carrier. The slurry was filtered and the resultant clear solution was used for exchange studies. Typically, the DMSO solution contained at this stage 1.3 · 10^{-3} mol l^{-1} F^-, with a water content of 85 ± 7 ppm, and a $^{18}F^-$ activity ranging from 0.5 to 1.0 mCi, at the beginning of the experiment. This method provides $^{18}F^-$ free of trace radionuclides other than ^{18}F and in yields of 50-60% of the $^{18}F-F_2$ activity used. Contact tim were generally 20 min. Slower flow rates and longer contact times improve the conversion efficiency.

Procedure

A measured aliquot (10 ml) of the $^{18}F^{-}$ solution was transferred into a glass vessel of slightly larger volume, equipped with a Teflon stopper that allowed insertion of a syringe needle without exposing the vessel contents to air.

The vessel was then allowed to reach the desired exchange temperature, within 0.1°C, in a thermostated silicone oil bath. The aromatic substrate, or substrates mixture, diluted if necessary with DMSO, was then added *via* the teflon stopper using a precision syringe of appropriate volume. Typically, the substrate concentration ranged from 0.02 to 0.15 mol l^{-1}. After thorough mixing, aliquots of the homogeneous exchanging solution were withdrawn at measured time intervals, quenched by cooling at -78°C and used for product analysis and kinetic measurements.

Analysis of the Products

The ^{18}F-labeled products are analyzed by radio glpc and radio hplc, using respectively a Hewlett-Packard model 7620A gas chromatograph, equipped with a hot-wire detector and connected to a heated flow proportional counter [12], and a Perkin Elmer Series 3 liquid chromatograph, equipped with a variable wavelength UV detector and connected to a Berthold HPLC Radioactivity Monitor, Model LB503 flow scintillation counter. The identity of the labeled products was established by comparison of their retention volumes with those of authentic, inactive samples on at least two columns of glpc, and with at least two different solvent systems in hplc. As an example, the ^{18}F-labeled hexafluorobenzene was identified and analyzed on the following columns: (i) a 4.6 meter dimethylsulfolane column operated at 40°C, (ii) a 3.6 meter Carbowax 1500 column operated at 65°C, (iii) a 1.8 meter β,β'-oxydipropionitrile column, operated at 30° and 45°C, and (iv) a 1.8 meter Apiezon "L" grease column, operated up to 210°C to detect any high-boiling radioactive products. Each column had 9.6 mm o.d. and 4.5 mm i.d.

The hplc was performed on a 25-cm ODS reversed-phase column, using water-acetonitrile mixtures as the eluent, the composition of the latter being systematically changed over a wide range, with different solvent and flow programs. Both glpc and hplc demonstrated the high radiochemical purity of the labeled substrate, no significant radioactive impurities being formed from any exchange reaction investigated.

Measurement of the Exchange Fraction

Owing to the unusually high radiochemical purity of the labeled products from the isotopic exchange, one could safely assume that the only radioactive species to be considered were $^{18}F^-$ and the ^{18}F-labeled polyfluorobenzene. This allowed a simple and direct procedure to be used in order to measure the extent of the isotopic exchange. The aliquots withdrawn from the exchange vessel at different times and quenched at low temperature were dissolved in an aqueous solution containing KF carrier and repeatedly extracted with benzene. The combined organic extracts were washed with water, and eventually the activity of the aqueous and organic extracts were measured with well-type scintillation counter. Decay corrections were made to allow intercomparison of data, taking into account the interval between the two measurements. The exchange fraction can be directly calculated from the activity of the labeled fluorobenzene and the residual activity of the inorganic fluoride. Control experiments, carried out with known activities of $K^{18}F$ and $C_6{}^{18}F_6$, showed that such a simple procedure was accurate and free from radiochemical artifacts.

In any event, the isotopic exchange was followed as well by radio glpc, measuring the growth of the ^{18}F activity in the initially inactive aromatic substrate. To this end, each sample withdrawn from the exchange vessel at a given time was subjected to radio glpc, and its specific activity was calculated from the response of the flow proportional counter (corrected for ^{18}F decay) and the response of the calibrated hot wire detector. In a few cases, a similar approach was followed, using hplc instead of glpc. While dynamic chromatographic techniques are less accurate, owing to the inherent limitations of flow counters, both chromatographic techniques give results consistent with those obtained with the extraction method. Analysis of the labeled products from the competition experiments must be of course carried out by radio chromatography.

RESULTS

The Labeled Products

Reaction of $^{18}F^-$ with C_6F_6, C_6H_5F, and the $C_6H_2F_4$ isomers leads exclusively to isotopic exchange, without formation of side products in detectable amounts, as shown by radio glpc and hplc. The results obtained with the latter technique are especially probative, excluding formation of high boiling products that would escape detection by glpc. The activity balance confirms that the ^{18}F-labeled substrate is the only product formed in measurable yields from all substrates investigated. On the other hand, radio gas chromatographic analysis revealed minute traces of $C_6{}^{18}F_6$ from the reaction of $^{18}F^-$ with C_6ClF_5 and C_6BrF_5, indicating occurrence of the ^{18}F-for-X substitution

$$^{18}F^- + C_6XF_5 \xrightarrow{k_X} X^- + {}^{18}F\text{-}C_6F_6 \qquad (1a)$$

which accompanies the predominant ^{18}F-for-F displacement.

$$^{18}F^- + C_6XF_5 \xrightarrow{k_F} F^- + {}^{18}F\text{-}C_6XF_5 \qquad (1b)$$

Process (1a) appears to be more significant for C_6ClF_5 than for C_6BrF_5, and therefore its dependence on the nature of X increases in the order H < Br < Cl. In any case, (1a) is a very minor reaction channel when compared to (1b), with a $k_X:k_F$ ratio well below 10^{-4}, and k_X values lower than 10^{-6} $l\ mol^{-1}s^{-1}$.

This result confirms the lack of reactivity of Cl and Br to participate in nucleophilic displacement by F^-, even in activated aromatic substrates and in suitable solvents [13].

Kinetic Features

The rate of appearance of the ^{18}F atoms in the initially inactive organic substrates follows the simple exponential law typical of isotopic exchange reactions. As an example, Figure 1, which relates to the exchange of $^{18}F^-$ with C_6HF_5 at 70°C, illustrates the linear dependence of log (1-F), where F denotes the exchange fraction on the reaction time. The rate measured at different concentrations of the reactants show that the isotopic exchange reaction obeys second-order kinetics over a wide range of concentrations.

Table I summarizes the specific rate constant for process (1b) for C_6XF_5 substrates, in the temperature range from 40° to 90°C. It should be noted that the values listed refer to overall exchange rates, and are not corrected for statistical factors. From the Table it is apparent that the rate constants are strongly dependent on the nature of the substituent, increasing in the order H < F < Br < Cl. A least squares treatment of the data of Table I gave the approximate Arrhenius parameters listed in Table II, which contains, for comparison purposes, the pertinent data concerning *ortho*- and *para*-fluoronitrobenzene, measured in the same solvent and within the same temperature range (40-70°C).

Comparison between the two classes of substrates shows that the exchange of polyfluorobenzenes is in general characterized by *higher* values of the activation energy, ranging from 19 to 28 Kcal mol^{-1} *versus* 19-20 Kcal mol^{-1} for fluoronitrobenzenes, a result consistent with the current views on substituent effects in aromatic nucleophilic displacement. Nevertheless, significant differences do exist in the preexponential factors as well, that can be traced, at least partially, to differential solvation effects in the course of the substitution on C_6XF_5, depending on the nature of the X group.

The specific rate constant for the isotopic exchange of tetrafluorobenzenes, measured at 70°C in competition experiments where C_6HF_5 was the references substrate, are given in Table III. The reactivity order is C_6HF_5 > 1,2,3,5-$C_6H_2F_4$ > 1,2,3,4-$C_6H_2F_4$ ≈ 1,2,4,5-$C_6H_2F_4$.

DISCUSSION

The nature of the labeled products, the kinetics of the isotopic exchange and the effects of the substituents on rate support a normal addition-elimination mechanism (S_NAr) with the first step being rate-determining.

The data suggest that the ^{18}F-for-F substitution involves the intermediacy of Meinsenheimer adducts, e.g. (II) from hexafluorobenzene.

Concerning the model substrate, C_6F_6, comparison of the kinetic constants shows that the activating effect of five F atoms approximately matches that of the nitro group in the *ortho* or the *para* position, in agreement with previously reported results concerning other nucleophilic substitutions [14]. Incidentally, the activating effect of the nitro group in the *ortho* and in the *para* position to the exchangeable F atom is roughly the same, as shown by the comparable reactivity of *o*- and *p*-nitrofluorobenzene toward $^{18}F^-$.

A detailed discussion of the substituent effects on the rate of isotopic exchange of the C_6XF_5 substrates would require direct knowledge of the orienting properties of X, which in turn would call for the measurement of the intramolecular distribution of ^{18}F in the labeled products. Unfortunately, such an experimental determination is prevented by the relatively short half-life of the tracer, and the discussion of the substituent effects must consequently be restricted to its qualitativ aspects.

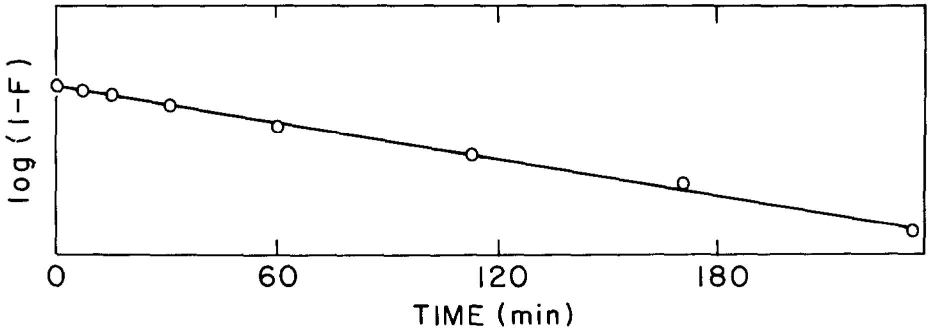


Fig. 1. Isotopic exchange of $^{18}F^-$ with C_6HF_5 in DMSO at 70°C
Logarithmic plot of 1-F *versus* the exchange time.

TABLE I

Second Order Rate Constants for the Isotopic Exchange of $^{18}F^-$ With C_6XF_5 Substrates in Dimethylsulfoxide (a)

X	10^3 k (l mol^{-1} s^{-1}) (b)					Relative Rates at 60°
	40°C	50°C	60°C	70°C	90°C	
H	0.03	0.13	0.47	1.5	-	1.0
Cl	2.2	6.0	20	60	-	43
Br	1.7	4.2	9.8	25	-	21
F	0.21	0.67	2.0	5.9	42	4.3

(a) For solvent composition, see text.

(b) Standard deviation of data ca. 10%.

TABLE II

Arrhenius Parameters for the Isotopic Exchange of $^{18}F^-$ With Polyfluoroarenes and Fluoronitrobenzenes in DMSO.(a)

Substrate	Arrhenius Equation(b)	Correlation Coefficient	$\Delta H^{\ddagger}$ Kcal mol^{-1}	$\Delta S^{\ddagger}$ cal mol^{-1} $degree^{-1}$
C_6HF_5	log k = 14.25 - 17.6 x	0.999	28	+ 7
C_6ClF_5	log k = 14.05 - 23.9 x	0.998	24	+ 3
C_6BrF_5	log k = 10.29 - 18.7 x	0.985	19	- 14
C_6F_6	log k = 13.14 - 24.0 x	0.990	24	- 1
o-$C_6H_4FNO_2$	log k = 10.79 - 19.4 x	0.973	19	- 11
p-$C_6H_4FNO_2$	log k = 11.07 - 20.5 x	0.961	20	- 10

(a) For solvent composition see text.

(b) $x = \frac{1000}{2,303\ RT}$, R in cal mol^{-1} $degree^{-1}$.

TABLE III

Second Order Rate Constants for the Isotopic Exchange of Isomeric Tetrafluorobenzenes With $^{18}F^-$ in DMSO at 70°C.(a)

Substrate	C_6HF_5	1,2,4,5-$C_6H_2F_4$	1,2,3,4-$C_6H_4F_2$	1,2,3,5-$C_6H_4F_2$
10^3 k (1 $mol^{-1}s^{-1}$)	1.5	< 0.01	< 0.01	0.065

(a) For solvent composition see text.

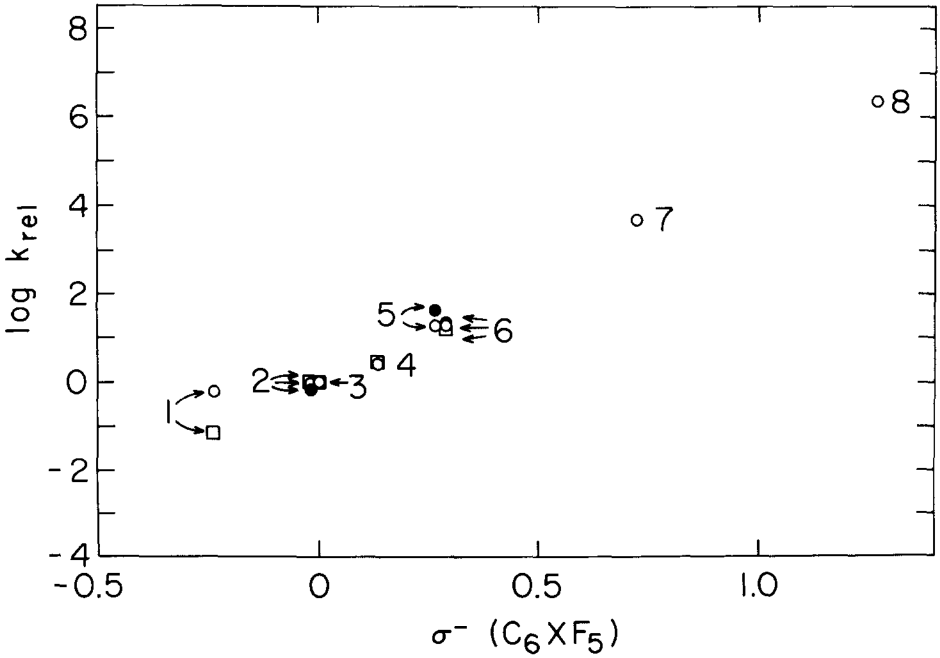


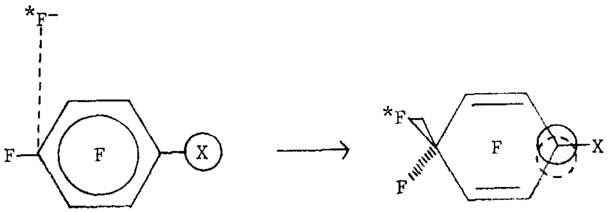
Fig. 2. Logarithm of the relative exchange rate *versus* the σ^- constant[18] for C_6XF_5 substrates.
o, MeO^- in MeOH at 60°C.[1g]; □ , MeO^- in MeOH/Dioxane at 50°.[1h]; ● , F^- in DMSO at 60°C, present work.
X = CH_3(1), F (2), (corrected for the statistical factor, see text), H (3), COO^- (4), Cl (5), Br (6), CF_3 (7), NO_2 (8).

A reasonable approach can proceed from the relative reactivity trend established for isomeric tetrafluorobenzenes, which provides inferential evidence for predominant activation of the ring positions *para* to the H atoms. The evidence is corroborated by the analogy with the nucleophilic substitution of the C_6XF_5 substrates (X = H, or halogens) by other reagents, notably methoxide ion, whose attack is known [15] to occur predominantly at the ring positions *para* to the X substituent. A logarithmic plot of the relative exchange rate at 60°C of C_6XF_5 substrates *versus* the σ^- constant of the X substituent is compared in Figure 2 with the analogous data concerning the reactivity of the same substrates toward the methoxide ion. While the scant data on the isotope exchange hardly justify any quantitative treatment, the similarity of the plots is nevertheless evident.

In this framework, the electronic effects of the substituent on the reactivity of the C_6XF_5 substrates, which follows the order $H \approx F < Br < Cl$ once allowance is made for the statistical factor, can be satisfactorily rationalized taking into account the I_π-repulsion effect [16,17]. In fact, the overall influence of a given substituent X on the reactivity of C_6XF_5 toward F^- can be considered as arising from the combination of two opposing effects:

a. The inductive effect of X, i.e. its ability to decrease the electron density at the *para* position, enhancing the rate of the F^- attack. The effect increases in the order $H << Br < Cl < F$.

b. The I_π effect, arising from the electrostatic repulsion between the non-bonding electron pairs of X and the negative charge developing at the ring position *para* to the reaction center on the C atom undergoing incipient sp^3 hybridization.



The I_π-repulsion effect, which tends to reduce the reaction rate, is known to increase in the order $H < Br < Cl < F$. Apparently, the Br, and especially the Cl substituent attain the most favorable combination of the two factors, in that their inductive effects are still sufficiently high, in contrast with that of H, while the I_π effect is not unduly large, as is probably the case for F.

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REFERENCES

1 (a) R. D. Chambers, Fluorine in Organic Chemistry, Wiley, New York 1973 275. (b) G. M. Brooke, J. Burdon, M. Stacey and J. C. Tatlow, J. Chem. Soc., (1960) 1768 and references therein. (c) J. Burdon, W. B. Hollyhead, and C. R. Patrick, J. Chem. Soc., (1964) 4663. (e) J. Burdon, W. B. Hollyhead and J. C. Tatlow, J. Chem. Soc. (1965) 5152. (f) J. G. Allen, J. Burdon and J. C. Tatlow, J. Chem. Soc., (1965) 6239. (g) J. Burdon, W. B. Hollyhead, C. R. Patrick and K. V. Wilson, J. Chem. Soc., (1965) 6375. (h) K. C. Ho and J. Miller, Austral. J. Chem., (1966), 19, 423. (i) R. D. Chambers, W. K. R. Musgrave, J. S. Waterhouse, D. L. H. Williams, J. Burdon, W. B. Hollyhead and J. C. Tatlow, J. Chem. Soc. Chem. Commun., (1974) 239. (l) R. Bolton and J. P. B. Sandall, J. Chem. Soc. Perkin II, (1976) 1541. (m) R. D. Chambers, J. S. Waterhouse and D. L. H. Williams, J. Chem. Soc. Perkin II, (1977) 585. (n) R. D. Chambers, D. Close, W. K. R. Musgrave, J. S. Waterhouse and D. L. H. Williams, J. Chem. Soc. Perkin II (1977) 1774. (o) R. D. Chambers, D. Close and D. L. H. Williams, J. Chem. Soc. Perkin II, (1980) 778.

2 For a scale of relative nucleophilicities, cfr. (a) J. Miller, Aromatic Nucleophilic Substitution, Elsevier, Amsterdam, 1968. See also: (b) M. J. V. De Oliveira Baptista and D. A. Widdowson, J. Chem. Soc. Perkin I, (1978) 295.

3 For a review, see: A. P. Wolf and J. S. Fowler, in Radiopharmaceuticals, Society of Nuclear Medicine, 1979, Vol. II, p. 13.

4 See for instance references 1c, 1g, 1h, 1i, 1l.

5 (a) G. A. Schmid and G. M. Hallman, J. Mol. Struct. 18 (1973) 489. (b) P. Cremaschi, A. Gamba and M. Simonetta, Theor. Chim. Acta, 25 (1972) 237. (c) A. J. Duke and R. F. Bader, Chem. Phys. Lett. 10 (1971) 631. (d) A. Dedrin and A. Veillard, J. Amer. Chem. Soc., 94 (1972) 6730. (e) A. Dedrin and A. Veillard, Chem. Phys. Lett., 5 (1970) 328. (f) H. B. Schlegel, K. Mislow, F. Bernardi and A. Bottoni Theor. Chim. Acta, 99 (1977) 7423. (h) S. Nagase and K. Morokosuma, J. Am. Chem. Soc., 100 (1978) 1666. (i) D. J. McLennan, Aust. J. Chem., 31 (1978) 1897.

6 J. Miller and A. J. Parker, J. Am. Chem. Soc., 83 (1961) 117.

7 (a) E. Buncell and H. Wilson, Adv. Phys. Org. Chem., (1977) 133. (b) R. Alexander, E. C. F. Ko, Y. C. Mac and A. J. Parker, J. Am. Chem. Soc. 89 (1967) 3703.

8 cfr. M. Fieser and L. F. Fieser, Reagents for Organic Reactions, Wiley, New York, 1967, Vol. I, p. 934.

9 cfr. C. D. Ritchie, G. A. Skinnger and V. G. Badding, J. Am. Chem. Soc., 89 (1967) 2063.

10 V. Casella, T. Ido, A. P. Wolf, J. S. Fowler, R. R. MacGregor and T. J. Ruth, J. Nucl. Med. 21 (1980) 750.

11 R. P. DeGrazio and R. G. Ange, US AEC-RFP-80, cf. Chem. Abst. 68 (1968), 26601a; Nucl. Sci. Abstr. 21 (1967) 23823.

12 M. Welch, R. Withnell and A. P. Wolf, Anal. Chem. 39 (1967) 275.

13 G. Fuller, J. Chem. Soc., (1965) 6264.

14 cfr. ref. 1g.

15 E. Nield, R. Stephens and J. C. Tatlow, J. Chem. Soc., (1959) 166. See also ref. 1g.

16 W. J. Hehre and J. A. Pople, J. Am. Chem. Soc., 94 (1972) 6801.

17 D. T. Clark, J. N. Murrell and J. M. Tedder, J. Chem. Soc., (1963) 1250.