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Copper(I) Catalysed Replacement of Bromine by Chloride Ion in Halonitrobenzenes. Part III.* Fluorine and Alkyl Substituted Bromonitrobenzenes

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The investigation of copper(I) catalysed bromine-chlorine exchange reactions of halonitrobenzenes in an aqueous hydrochloric acid—acetic acid medium, kinetically studied in Parts I and II, has now been extended to 2-bromo-3-fluoro- and 2-bromo-5-fluoronitrobenzenes and 2-bromo-3-methyl-, 2-bromo-3-ethyl-, 2-bromo-3-*t*-butyl- and 2-bromo-5-methylnitrobenzenes. It is further confirmed that chiefly steric but also polar effects account for the activation of the substituent in the 3-position. Some deactivating effect of the alkyl groups, probably of polar character, as compared to halogens of comparable size in the 3-position, is indicated. Activation parameters and mechanistic aspects of the results are given.

In Parts I [1] and II [2] of the present series the copper(I) catalysed bromine-chlorine exchange reactions were studied under homogeneous conditions at 80 – 100 °C in an aqueous hydrochloric acid – acetic acid medium with a chloride ion concentration of 5.25 M and with the experimental conditions described in Ref. 1. The dichlorocuprate(I) ion was found to be the catalysing species in the second-order rate of substitution. The observed large accelerating effect of an *ortho* nitro group and the insensitivity of the rate of substitution to the nature of the *para* substituent, together with the observed effect of halogen in the other position *ortho* to the reaction site, and the large negative entropies (– 173 to – 155 J/K mol) and low enthalpies (45 – 51 kJ/mol)[1–3], indicating a high degree of order in the transition state, led to the suggestion of a tetrahedral intermediate, in which the *ortho* nitro group and the halogen to be replaced interact with the dichlorocuprate(I) ion. Similar observations have been made for other copper-assisted reactions, *e.g.* the Ullmann biaryl synthesis,[4] copper-promoted decarboxylation,[5] and reactions between aryl halides and copper(I) salts [6] or copper(I) acetylides.[7] The entropies of activation found for copper-promoted decarboxylation are – 167 to – 109 J/K mol [5] and for reactions between aryl halides and copper(I) acetylides – 264 to – 121 J/K mol.[7]

The rate for copper(I) catalysed bromine-chlorine exchange was found to be three times larger than the rate of the corresponding iodine-chlorine exchange.[3] In view of this result, it does not seem very likely that the rate-determining step involves breaking of the carbon-bromine and the carbon-iodine bonds in the aryl halides.

The study of *ortho* halogen effects, previously comprising iodine, bromine, and chlorine has now been completed with an investigation of fluorine. A similar study of the effect of an *ortho* alkyl group has also been performed in this work, because it seemed important to compare the effect on the exchange rate of an *ortho* substituent with a negative σ_0-value with the effect of the halogens. The alkyl groups selected for examinations were methyl, ethyl, and *t*-butyl. A methyl group has about the same size (van der Waals volume 13.7 cm³/mol) as chlorine and bromine (12 and 15.1

* For Part II, see Ref. 2.

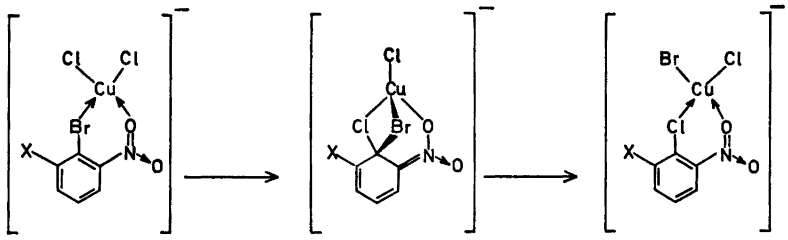

Fig. 1. Bromide – chloride exchange.

cm ^{3}/mol, respectively). The ethyl group has a van der Waals volume of 23.9 cm ^{3}/mol [8] but is not symmetrical and can adjust itself to a more favourable position; its effective size is about the same as that of the methyl group.

RESULTS AND CALCULATIONS

The compounds kinetically studied in this work were 2-bromo-3-fluoronitrobenzene, 2-bromo-5-fluoronitrobenzene, 2-bromo-3-methylnitrobenzene, 2-bromo-5-methylnitrobenzene, 2-bromo-3-ethylnitrobenzene, and in view of the difficulties in its preparation to a limited extent 2-bromo-3-*t*-butylnitrobenzene. The copper(I) catalysed bromine-chlorine exchange of these compounds was studied at 80 – 100 °C.[1] The corresponding 2-chloro compounds were synthesized for calibration purposes.

The exchange mixture was analyzed by GLC, and in the case of 2-bromo-3-fluoronitrobenzene, the starting material and the exchange product 2-chloro-3-fluoronitrobenzene, were isolated together with about 5 % of two by-products which were identified by their mass spectra. The by-products were almost certainly 2-chloro-3-fluoroaniline and 2-bromo-3-fluoroaniline and their identities were indicated by a 3:1 doublet at *m/e* 145 and 147, and by a 1:1 doublet at *m/e* 189 and 191, respectively. Such a reduction of the nitro group has always been observed in the copper(I) catalysed exchange reactions investigated by the present author. Traces at *m/e* 141 revealed fluoronitrobenzene, obviously arising from reductive dehalogenation of 2-bromo-3-fluoronitrobenzene. Reductive dehalogenation has not been noted previously in the bromine-chlorine exchange reactions, but has been detected in the iodine-chlorine exchange mixture.[3] Bacon and Wright [9] observed that in copper(I) catalysed exchange reactions between sodium methoxide and bromo- and iodobenzene derivatives, the iodides were more responsive to reduction than the bromides. Reductive dehalogenation in the presence of a hydrogen donor has also been reported by Fanta [4] and by Nilsson and Björklund.[10] The bromine-chlorine exchange was very slow for 2-bromo-5-fluoronitrobenzene, and the reduction of the nitro group became a competitive reaction. The mass spectrum showed a 1:1 doublet, centered at 190 *m/e*, indicating 2-bromo-5-fluoroaniline.

In the exchange mixture from 2-bromo-3-methylnitrobenzene about 3 % of by-products were detected by GLC, the mass spectra showing a 1:1 doublet at *m/e* 185 and 187 and traces of a 3:1 doublet at *m/e* 141 and 143, due to 2-bromo-3-methylaniline and 2-chloro-3-methylaniline, respectively.

From 2-bromo-5-methylnitrobenzene, about 2 – 3 % of 2-bromo-5-methylaniline was detected in the reaction mixture; the mass spectrum had a 1:1 doublet at *m/e* 185 and 187.

For 2-bromo-3-ethylnitrobenzene the by-products were 2-bromo-3-ethylaniline (2 – 3 %) and traces of 2-chloro-3-ethylaniline as seen from the mass spectra with molecular ions at *m/e* 199 and 201 in the proportions 1:1 and at *m/e* 155 and 157 in the proportions 3:1, respectively.

2-Bromo-3-*t*-butylnitrobenzene was only studied at 98 °C because of the difficulty mentioned above and its poor solubility at lower temperatures in the medium. The compound resulting from the copper(I) catalysed bromine-chlorine exchange of 2-bromo-3-*t*-butylnitrobenzene had to be identified by its

mass spectrum: a 3:1 doublet at *m/e* 213 and 215 was assumed to indicate 2-chloro-3-*t*-butylnitrobenzene.

When the degassed reaction mixture of 2-bromo-3-methylnitrobenzene with copper(I) chloride present was subjected to irradiation at 350 nm for 2 h at about 30 °C, the reduction of the nitro group dominated over the bromine-chlorine exchange, which did not increase its rate compared to an experiment with copper(I) chloride in the dark at 30 °C. When a solution without copper(I) was irradiated, the only observed reaction was a very slight bromine-chlorine exchange and when this solution was stored in the dark neither exchange nor reduction occurred.

The nature of the side reactions, the dehalogenation and the reduction of the nitro group, will be further described in a subsequent paper.[11]

No nuclear coupling products were observed in the reaction mixture within the limits of detection (< 1 %).

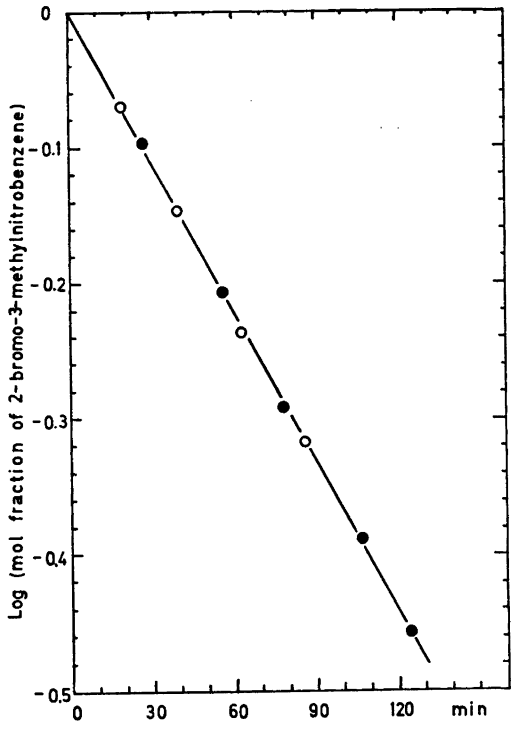

Fig. 2. Two representative runs (● and ○, respectively) of bromine-chlorine exchange in 2-bromo-3-methylnitrobenzene at 98 °C.

The pseudo first-order kinetics are illustrated in Fig. 2 for 2-bromo-3-methylnitrobenzene at 98 °C. The rate constant k_{obs} was calculated from the slope of the lines by the method of least squares and the second-order rate constant k_2 from an estimation of $[CuCl_2^-]$ as described in Ref. 1. The results are summarized in Table 1, together with some values from previous work for comparison.

The activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were calculated from k_2 according to the Eyring equation (see Ref. 1)

$$k_2 = \frac{\varkappa kT}{h} \exp(-\Delta H^{\ddagger}/RT) \exp(\Delta S^{\ddagger}/R)$$

and are presented in Table 2. The transmission coefficient $\varkappa$ is assumed to be unity. The reversibility of the bromine-chlorine exchange was investigated in Ref. 2 and was found not to complicate the interpretation to any marked extent.

DISCUSSION

Steric effects will speed up a reaction if there is a decrease in crowding in going from the reactants to the transition state. The increase of the rate of the exchange is very nicely parallelled by the increasing van der Waals volume of the halogen in the 3-position, as seen from Table 1.

Changes in $\Delta S^{\ddagger}$ are parallelled by changes in $\Delta H^{\ddagger}$ making the resulting effect on reactivity less pronounced. The entropies and enthalpies of activation for the 3-chloro-, 3-bromo-, and 3-iodo-2-bromonitrobenzenes are seen from Table 2 to be very close to one another, while the 3-fluoro compound shows lower values for both parameters.

Steric effects may be small for the fluorine atom with a van der Waals volume of 5.8 cm^3/mol; fluorine requires only slightly more space than a hydrogen atom (van der Waals volume = 3.4 cm^3/mol).[8]

The σ_0-values for chlorine, bromine, and iodine are of the same magnitude, but fluorine displays a lower value due to its larger mesomeric effect, characteristic of second row elements (see Ref. 2). This resonance effect of the fluorine atom is very well demonstrated in the ^1H NMR spectrum of 2-bromo-5-fluoronitrobenzene ($CDCl_3$): δ 7.73 (H-3), 7.19 (H-4),

Table 1. Rate parameters in copper(I) catalysed bromine-chlorine exchange in bromonitrobenzenes. For experimental conditions see Ref. 1.

$[Cu^+]_{tot} = 0.1124$ M, $[Cl^-] = 5.25$ M.

Compound [a]	Temp./ °C [b]	$CuCl_2^-$/ M [c]	k_{obs}/ 10^{-4} s^{-1} [d]	k_2/ 10^{-4} l mol^{-1} s^{-1} [e]	van der Waals [g] volume/cm^3 mol^{-1} of 3-X.
2-Bromo-3-fluoronitrobenzene	79.95	0.056	0.401 ± 0.010	7.13	
2-Bromo-3-fluoronitrobenzene	89.98	0.063	0.662 ± 0.018	10.53	5.8
2-Bromo-3-fluoronitrobenzene	98.05	0.076	1.000 ± 0.010	13.11	
2-Bromo-5-fluoronitrobenzene	89.98	0.063	~0.14 ± 0.006	~2	
2-Bromonitrobenzene [f]	89.98	0.063	~0.28	~4	3.4
2-Bromo-3-chloronitrobenzene [f]	89.98	0.063	1.28	20.4	12.0
2,3-Dibromonitrobenzene [f]	89.98	0.063	1.83	29.2	15.1
2-Bromo-3-iodonitrobenzene [g]	89.98	0.063	2.43	38.7	19.6
2-Bromo-5-chloronitrobenzene [f]	89.98	0.063	~0.22	~3	
2-Bromo-3-methylnitrobenzene	79.95	0.056	0.439 ± 0.000	7.82	
2-Bromo-3-methylnitrobenzene	89.98	0.063	0.878 ± 0.006	13.98	13.7
2-Bromo-3-methylnitrobenzene	98.05	0.076	1.410 ± 0.010	18.49	
2-Bromo-3-ethylnitrobenzene	79.95	0.056	0.393 ± 0.004	6.99	
2-Bromo-3-ethylnitrobenzene	89.98	0.063	0.727 ± 0.005	11.57	23.9
2-Bromo-3-ethylnitrobenzene	98.05	0.076	1.262 ± 0.019	16.54	
2-Bromo-3-*t*-butylnitrobenzene	98.05	0.076	2.602 [h]	34.11	44.3
2-Bromo-5-methylnitrobenzene	89.98	0.063	0.237 ± 0.006	3.78	

[a] 0.562 M. [b] Accuracy ± 0.05. [c] Estimated from the data in Ref. 1. [d] Pseudo first-order rate constant. [e] Second-order rate constant, calculated on substrate and $CuCl_2^-$ as reacting species. [f] Values from Part I.[1] [g] Values from Part II.[2] [h] Values from two runs, which have been combined.

7.58 (H-6). H-6 *ortho* to the fluorine and the nitro group is more shielded than H-3, *ortho* to the bromine atom, and displaced upfield. The corresponding values for 2-bromo-5-chloronitrobenzene: δ 7.72 (H-3), 7.42 (H-4), 7.85 (H-6). The ^1H NMR spectra of 2-fluoro-6-nitroaniline and 2-chloro-6-nitroaniline also demonstrate this resonance effect: δ 7.2 [7.54] (H-3), 6.6 [6.67] (H-4), 7.9 [8.11] (H-5). The values in brackets are for the chloro compound.

2-Bromo-3-fluoronitrobenzene reacts twice as fast as 2-bromonitrobenzene. The difference is probably due to the polar effect of the fluoro atom rather than to a steric effect. 2-Bromo-3-fluoronitrobenzene is five times more reactive than 2-bromo-5-fluoronitrobenzene, probably because of the greater inductive effect of the fluorine atom in the *ortho* position. However, it should be borne in mind that the rates of exchange are influenced by solvation effects, and that the differences in rate are quite small.

Table 2. Activation enthalpies and entropies for 3-substituted 2-bromo-nitrobenzenes.

Compound	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J K^{-1} mol^{-1}
2-Bromo-3-fluoronitrobenzene	34 ± 7 [c]	−211 ± 19 [c]
2-Bromo-3-chloronitrobenzene [a]	45 ± 6	−173 ± 18
2,3-Dibromonitrobenzene [a]	51 ± 4	−155 ± 11
2-Bromo-3-iodonitrobenzene [b]	46 ± 3	−168 ± 10
2-Bromo-3-methylnitrobenzene	49 ± 10	−166 ± 27
2-Bromo-3-ethylnitrobenzene	49 ± 3	−168 ± 8

[a] Values from Part I.[1] [b] Values from Part II.[2] [c] The errors are 3 S.E. from the least-squares method calculations.

The results in Table 1 also demonstrate the deactivating effect of an *ortho* alkyl group on the exchange rate, as compared to an *ortho* halogen atom of comparable size; see above. The electron-releasing effect of an *ortho* alkyl group should make the proposed negatively charged transition state[1] to be energetically less favourable than that for an *ortho* halogen compound.

The polar effects of the methyl and ethyl groups are comparable. This is also true for their steric effects, as discussed above. Both polar and steric effects are reflected in the rates of the bromine-chlorine exchange for 2-bromo-3-ethyl- and 2-bromo-3-methylnitrobenzenes in comparison with the halogen compounds, as seen in Table 1. However, the much larger *t*-butyl group increases the rate of exchange by a factor of two in comparison with methyl and ethyl.

The enthalpies of activation, $\Delta H^{\ddagger}$, and the entropies of activation, $\Delta S^{\ddagger}$, for the 3-methyl- and 3-ethyl-2-bromonitrobenzenes are of the same magnitude as those for the 3-bromo-, 3-chloro- and 3-iodo-2-bromonitrobenzenes; see Table 2.

The mechanisms of copper-promoted reactions, such as the Ullmann biaryl synthesis, copper-catalysed decarboxylation, copper-catalysed halogen exchange and the accompanying reductive dehalogenation, has been the subject of much speculation. Do they have a common intermediate step? It is assumed by Nilsson[12] that the Ullmann biaryl synthesis and copper-promoted decarboxylation proceed *via* a common intermediate, an arylcopper. Reductive dehalogenation often accompanies the Ullmann synthesis, especially in the presence of hydrogen donors. This fact may be taken as evidence for an intermediate arylcopper species.[10]

Cohen *et al.*[13] propose an oxidative addition – reductive eliminition reaction *via* a transient organocopper(III) intermediate in the exchange reactions of aryl halides with salts of copper(I):

$$\mathrm{ArI} + \mathrm{CuCl} \rightarrow \mathrm{ArCuCl^{(III)}I} + 2e^- \quad (1)$$

$$\mathrm{ArCuCl^{(III)}I} + 3\mathrm{CuCl} \rightarrow \mathrm{ArCu} + 2\mathrm{CuCl_2} + \mathrm{CuI} \quad (2)$$

$$\mathrm{ArCu} + 2\mathrm{CuCl_2} \rightarrow \mathrm{ArCu^{(III)}Cl_2} + 2\mathrm{CuCl} \quad (3)$$

$$\mathrm{ArCuCl_2} + 2e^- \rightarrow \mathrm{ArCl} + \mathrm{CuCl} \quad (4)$$

This proposal could account for the exchange reactions taking place in an organic solvent. But do the organocopper(III) intermediates agree with the experience from the investigations by the present author of copper(I) catalysed exchange reactions in aqueous media? Copper(III) complexes have a quadratic or octahedral configuration;[14] complexes with halogen, including fluorine, are known. These configurations of an intermediate complex could hardly explain the observed accelerating effect, correlated to the van der Waals volume, of the substituent *ortho* to the reaction center. In addition, organocopper has the tendency to give coupling products and to be protonated to the arene by carboxylic acids. Biaryl products have never been detected, and dehalogenation products are only obtained as by-products in a few cases in the present series of investigations, see above. On the other hand a tetrahedral intermediate copper(I) – aryl halide complex could explain the reported accelerating effect of an *ortho* substituent, because strain is released, and a transition state of similar kind may also justify the large negative $\Delta S^{\ddagger}$ values (Table 2). The assumption of an intermediate copper(I) complex is also supported by the failure of 3-bromo-2-fluoronitrobenzene to exchange fluorine for chlorine[15] considering the fact that copper(I) fluoride complexes are unknown. Therefore the proposed negatively charged, tetrahedral $CuCl_2^-$-aryl halide complex cannot be rejected as an intermediate and as an approximate model for the transition state until experiments can be shown to support an other mechanism.

One can, however, not exclude the possibility that, when the conditions are altered, some other mechanism could prevail in the halogen exchange reaction. For instance when 2-bromo-3-methylnitrobenzene was irradiated without copper(I) chloride present, traces of the halogen exchange product, 2-chloro-3-methylnitrobenzene, were still observed.

EXPERIMENTAL

Melting points were determined on a Kofler Hot-Stage Microscope. ^{1}H NMR spectra were obtained with a Varian A-60 instrument (TMS as internal standard) and IR spectra with a Beckman IR-9 spectrophotometer. The mass spectra were performed on an LKB A 9000

instrument and the ^{19}F NMR spectrum on a Varian XL-100-15 spectrometer at Instrumentstationen, The Chemical Center, University of Lund.

All calculations were carried out on an Olivetti Programma 101 electronic desk-top computer.

2-Fluoroacetanilide. 2-Fluoroaniline (55.6 g, 0.5 mol, Fluka AG, *purum*) dissolved in 50 ml of benzene, was acetylated with 53 g (0.52 mol) of acetic anhydride. Yield 61.8 g (81 %), m.p. 77.5 – 78.5 °C, lit.[16] 79 °C.

2-Fluoro-6-nitroaniline. 2-Fluoroacetanilide (45.9 g, 0.3 mol) was nitrated according to the method of Franzén and Engel [17] for nitration of 2-bromoacetanilide. The isomeric mononitration products (38 g, 64 %) were separated by agitating the crude material with 450 ml of ice cold "Witt-Utermann solution" as described by Gibson and Johnson.[18] The 2-fluoro-4-nitroacetanilide was only slightly soluble in this solution and was filtered off. After 24 h only 1.5 g of hydrolysed material, 2-fluoro-4-nitroaniline, m.p. 135 – 136 °C, lit.[19] 134 – 135 °C, had precipitated. Treatment of the filtrate with acetic acid gave a precipitate of 9.45 g (16 %) of 2-fluoro-6-nitroacetanilide, m.p. 183 – 184 °C, lit.[20] 182.5 – 183.0 °C. On boiling a solution of this compound in 45 ml of ethanol and 22 ml of hydrochloric acid for 3 h, hydrolysis took place, and 6.65 g (89 %) of 2-fluoro-6-nitroaniline was obtained after dilution with water and filtration; m.p. 75.5 – 76.5 °C, lit.[20] 75 – 76 °C. The yield was 14 % calculated on the 2-fluoroacetanilide.

^1H NMR spectrum in $CDCl_3$: δ 7.2 (H-3, octet), 6.6 (H-4, octet), 7.9 (H-5, octet) 6.12 (NH_2, s). J_{3-4} 7.8 Hz, J_{3-5} 1.5 Hz, J_{4-5} 8.7 Hz, J_{3-F} 10.7 Hz, J_{4-F} 5.5 Hz and J_{5-F} 1.5 Hz.

2-Bromo-3-fluoronitrobenzene was synthesized from the preceding compound by a modification of a procedure by Gunstone and Tucker [21] (see Ref. 2). The 2-fluoro-6-nitroaniline (4.7 g, 0.03 mol) gave a yield after steam distillation of 4.75 g (72 %) of 2-bromo-3-fluoronitrobenzene, m.p. 42 – 43 °C. We have not been able to find the compound in the literature. The mass spectrum showed a 1:1 doublet at *m/e* 219 and 221, as expected for the desired compound.

2-Chloro-3-fluoronitrobenzene was prepared by the procedure described above for 2-bromo-3-fluoronitrobenzene. The 2-fluoro-6-nitroaniline (0.03 mol) gave a yield of 2.7 g (52 %) of 2-chloro-3-fluoronitrobenzene, m.p. 29.5 – 30.5 °C after recrystallization from methanol. Its boiling point is given in the literature [22] but not its melting point. The mass spectrum had a 3:1 doublet centered at *m/e* 176, the molecular weight of 2-chloro-3-fluoronitrobenzene.

4-Fluoroacetanilide. 4-Fluoraniline (22.2 g, 0.2 mol, Fluka AG, *pract.*) dissolved in 30 ml of benzene, was acetylated with 0.21 mol (21.4 g) of acetic anhydride. The yield of 4-fluoroacetanilide was 28.6 g (94 %), m.p. 153.5 – 154.5 °C, lit.[23] 150.5 – 151.5 °C.

4-Fluoro-2-nitroaniline was produced from 4-fluoroacetanilide by the same nitration procedure as described above for 2-fluoro-6-nitroaniline. 4-Fluoroacetanilide (7.65 g, 0.05 mol) gave 8.1 g (82 %) of the crude 4-fluoro-2-nitroacetanilide. After recrystallization from methanol, the m.p. was 72 – 73 °C, lit.[24] 72 – 73 °C. Hydrolysis of the acetanilide and subsequent steam distillation gave 4.7 g of 4-fluoro-2-nitroaniline (61 % calculated on the 4-fluoroacetanilide); m.p. 93 – 94 °C, lit.[25] 93 – 94 °C.

2-Bromo-5-fluoronitrobenzene was synthesized from 4-fluoro-2-nitroaniline by the same procedure as described for 2-bromo-3-fluoronitrobenzene. An amount of 3.12 g (0.02 mol) of the amine yielded 3.35 g of the bromo compound (76 %), m.p. 40 – 41 °C, lit.[26] 39.5 – 40.0 °C. The mass spectrum revealed a 1:1 doublet at *m/e* 219 and 221.

^1H NMR ($CDCl_3$ and $(CD_3)_2CO$ [in brackets]): δ 7.73 [7.9] (H-3, q), 7.19 [7.4] (H-4, oct), 7.58 [7.8] (H-6, q).

$J_{3-4} = 8.9$ Hz [8.95], $J_{4-6} = 2.9$ Hz [2.95], $J_{4-F} = 7.45$ Hz [7.85].

$J_{3-F} = 5.1$ Hz [5.2] and $J_{6-F} = 7.65$ Hz [7.95].

^{19}F NMR spectrum in $(CD_3)_2CO$: $J_{F-H_3} =$ 5.1 Hz and $J_{F-H_6,\ F-H_4} = 7.9$ Hz (octet).

2-Chloro-5-fluoronitrobenzene was prepared from 4-fluoro-2-nitroaniline following the description for 2-chloro-3-fluoronitrobenzene. 1.56 g (0.01 mol) gave after steam distillation a yield of 1.15 g (66 %) of 2-chloro-5-fluoronitrobenzene, m.p. 37.0 – 38.5 °C, lit.[27] 36 °C. The mass spectrum had a 3:1 doublet at *m/e* 175 and 177.

2-Chloro-6-nitroaniline (for NMR study) was synthesized from 2-chloroaniline (Fluka AG, *puriss*) by means of acetylation, nitration and hydrolysis as described above for 2-fluoro-6-nitroaniline; yield 33 % of 2-chloro-6-nitroaniline (calculated on the acetanilide), m.p. 75 – 76 °C, lit.[1] 75.5 – 76.0 °C.

^1H NMR ($CDCl_3$): δ 7.54 (H-3, q), 6.67 (H-4, q), 8.11 (H-5, q), 6.6 (NH_2, s). $J_{3-4} =$ 7.7 Hz, $J_{4-5} = 8.7$ Hz and $J_{3-5} = 1.6$ Hz.

2-Bromo-5-chloronitrobenzene (for NMR study) was prepared as described in Ref. 1.

^1H NMR ($CDCl_3$): δ 7.72 (H-3, d), 7.42 (H-4, q), 7.85 (H-6, d), J_{3-4} 8.4 Hz and J_{4-6} 2.2 Hz.

2-Methylacetanilide. 2-Methylaniline (107 g, 1 mol), dissolved in 100 ml of benzene, was acetylated with 105 g of acetic anhydride (1.03 mol); yield 124.9 g (84 %), m.p. 109 – 110 ° C, lit.[28a] 110 °C.

2-Methyl-6-nitroaniline. The preceding compound (112 g, 0.75 mol) was subjected to the procedure described for the preparation of 2-fluoro-6-nitroaniline. The mononitrated isomers were separated with 3000 ml of Witt-Utermann solution. The 4-nitro-isomer was almost insoluble and was filtered off (35 g

of 2-methyl-4-nitroacetanilide, m.p. 203.5–204.5 °C, lit.[29] 201 °C). The isomer 2-methyl-6-nitroacetanilide (70 g) m.p. 159.0–159.5 °C, lit.[29] 160 °C, was hydrolysed in an ethanol-hydrochloric acid solution (2:1) by boiling for 8 h. After steam distillation 38.6 g of 2-methyl-6-nitroaniline, m.p. 95.5–96.5 °C, lit.[28b] 97 °C, was obtained; yield 34 % based on 2-methylacetanilide.

^{1}H NMR ($CDCl_3$): δ 7.27 (H-3, q), 6.6 (H-4, q), 7.98 (H-5, q), 2.26 (CH_3, s), 5.7 (NH_2, s). $J_{3-4}=6.9$ Hz, $J_{4-5}=8.2$ Hz, and $J_{3-5}=1.5$ Hz.

2-Bromo-3-methylnitrobenzene. 2-Methyl-6-nitroaniline (15.2 g, 0.1 mol) was diazotized and subjected to a Sandmeyer reaction as described for the preparation of 2-bromo-3-fluoronitrobenzene. The yield after steam distillation was 15.15 g of 2-bromo-3-methylnitrobenzene (71 %). After two recrystallizations from methanol the m.p. was 40.0–41.5 °C, lit.[30] 41–42 °C. The mass spectrum showed a doublet, 1:1, at *m/e* 215 and 217, indicative of the desired substance.

^{1}H NMR ($CDCl_3$, Bruker WH 270 instrument): δ 7.43 (H-4, q), 7.33 (H-5, q), 7.50 (H-6, q), 2.48 (CH_3, s). $J_{4-5,\ 5-6}=7.65$ Hz.

2-Chloro-3-methylnitrobenzene. 2-Methyl-6-nitroaniline (15.2 g, 0.1 mol) was subjected to the same procedure as described for the preparation of 2-chloro-3-fluoronitrobenzene. After steam distillation the yield was 12.6 g (74 %). After two recrystallizations from methanol the m.p. was 23–24 °C, lit.[31] 23 °C. The mass spectrum had a 3:1 doublet at *m/e* 171 and 173.

2-Bromo-5-methylnitrobenzene was synthesized from 4-methyl-2-nitroaniline (Fluka AG, *pract.*) as described above for 2-bromo-3-methylnitrobenzene. From 7.6 g (0.05 mol) of the amine the yield was 7.8 g (72 %). After one recrystallization from hexane and two from methanol the m.p. was 31.5–32.0 °C, lit.[32] 31.5–32.5 °C. The mass spectrum showed a 1:1 doublet at *m/e* 215 and 217.

^{1}H NMR ($CDCl_3$): δ 7.58 (H-3, d), 7.23 (H-4, q), 7.64 (H-6, d)), 2.38 (CH_3, s). $J_{3-4}=$ 7.8 Hz and $J_{4-6}=1.7$ Hz.

2-Chloro-5-methylnitrobenzene was synthesized from the same 4-methyl-2-nitroaniline by the method used for the preparation of 2-chloro-3-methylnitrobenzene. The yield was 79 % after steam distillation. After two recrystallizations from hexane and two from methanol the m.p. was 6–7 °C, lit.[33] 7 °C. The mass spectrum had a 3:1 doublet at *m/e* 171 and 173.

2-Ethylacetanilide was prepared from 84.8 g (0.7 mol) of 2-ethylaniline (Fluka AG, *pract.*) in 70 mol of benzene by acetylation with 75 g of acetic anhydride (0.73 mol). The yield of 2-ethylacetanilide was 108 g (95 %), m.p. 113–114 °C, lit.[34] 113–114 °C.

2-Ethyl-6-nitroaniline was prepared from the preceding compound by the method described for the methyl compound. An amount of 40.8 g (0.25 mol) was nitrated, and the mixture of 6- and 4-mono-nitrated isomers was separated by grinding with Witt-Utermann solution. By this procedure 22 g of 2-ethyl-6-nitroacetanilide was obtained (42 %), m.p. 161.5–163.5 °C, lit.[35] 164–166 °C. After hydrolysis in boiling ethanol-hydrochloric acid (2:1) and steam distillation 12.4 (30 %) of 2-ethyl-6-nitroaniline was obtained, m.p. 30.5–31.0 °C, lit.[35] 31–32 °C. 2-Ethyl-4-nitroacetanilide (11 g) was left insoluble in the Witt-Utermann solution. It had m.p. 152.5–154.5 °C, lit.[36] 155 °C, and 6.6 g was hydrolysed and filtered off as 2-ethyl-4-nitroaniline, m.p. 86.5–87.5 °C, lit.[37] 86.0–87.5 °C. Contrary to the report by Hansch ,[35] the separation of the isomers by Witt-Utermann solution proved to be successful.

^{1}H NMR of the 6-nitro compound ($CDCl_3$): δ 7.28 (H-3, q), 6.63 (H-4, q), 8.0 (H-5, q), 1.28 (CH_3, t), 2.57 (CH_2, q), 6.28 (NH_2, s). $J_{3-4}=6.9$ Hz, $J_{3-5}=1.4$ Hz and $J_{4-5}=8.3$ Hz.

2-Bromo-3-ethylnitrobenzene was prepared from 2-ethyl-6-nitroaniline as described for 2-bromo-3-fluoronitrobenzene. A yield of 6 g (75 %) after steam distillation was obtained from 5.8 g (0.035 mol) of starting material. After four recrystallizations from methanol the m.p. was −3.5 to −3 °C. We have not been able to find the compound described in the literature. The mass spectrum showed a 1:1 doublet at 229 and 231 *m/e*.

^{1}H NMR ($CDCl_3$, Bruker WH 270 instrument): δ 7.43 (H-4, q), 7.37 (H-5, q), 7.48 (H-6, q), 1.23 (CH_3, t), 2.83 (CH_2, q). $J_{4-5,\ 5-6}=$ 7.55 Hz and $J_{4-6}=1.8$ Hz.

2-Chloro-3-ethylnitrobenzene was prepared from the same aniline by the method described for 2-chloro-3-fluoronitrobenzene. An amount of 2.35 g (0.014 mol) of the aniline gave 1.8 g (70 %) of 2-chloro-3-ethylnitrobenzene, m.p. 1 °C after steam distillation. Hansch [35] has described the compound as a yellow liquid. The compound was recrystallized twice from methanol. The mass spectrum showed a 3:1 doublet at *m/e* 185 and 187.

^{1}H NMR ($CDCl_3$, Bruker WH 270 instrument): δ 7.45 (H-4, q), 7.32 (H-5, q), 7.58 (H-6, q), 1.24 (CH_3, t), 2.85 (CH_2, q). $J_{4-5,\ 5-6}=$ 7.7 Hz and $J_{4-6}=1.65$ Hz.

2-t-Butylnitrobenzene was prepared from 402 g (3 mol) of *t*-butylbenzene (Fluka AG, *purum*) according to a procedure described by Craig.[38] The crude yield of a mixture of mono-nitrated isomers was 525 g (98 %). From GLC and NMR it was seen that about 15 % was the desired *ortho* isomer and about 75 % was the *para* isomer. In contrast to the report by Craig a third product with a mass spectrum showing the molecular ion at *m/e* 179 was found, indicating the 3-nitro-*t*-butylbenzene. Nelson and Brown [39] also report *o*-, *m*- and *p*-isomers in the proportions 16:11:73 in their nitration of *t*-butylbenzene. The isomeric mixture was distilled twice in a spinning-band column and 40 g of the *ortho* isomer, of 96 % purity, was

isolated, b.p. 109–111 °C at 1.60 kPa. The yield was about 8 %, lit.[39] b.p. 115.5 °C at 1.33 kPa, lit.[40] b.p. 67 °C at 0.053 kPa. The impurity was the *meta* isomer.

2-t-Butylacetanilide. 30.15 g (0.17 mol) of 2-*t*-butylnitrobenzene was reduced with 28.5 g (0.51 mol) of iron powder in 50 % aqueous ethanol, acidified with hydrochloric acid, following a description of Mahood *et al.*[41] The crude yield was 21.5 g (85 %). The crude 2-*t*-butylaniline (15 g, 0.1 mol) dissolved in 20 ml of benzene, was acetylated with 10.5 g of acetic anhydride (0.105 mol); yield 17.2 g (90 %), m.p. 163–164 °C, lit.[42a] 160–161 °C, lit.[42b] 166–168 °C.

2-t-Butyl-6-nitroaniline. The preceding compound (17.2 g, 0.09 mol) was nitrated as described for the methyl compound with a mixture of 23.5 ml of nitric acid ($d = 1.52$) and 12.6 ml of glacial acetic acid at 0 °C. The mixture was left for 48 h at room temperature and was then poured into 300 ml of ice-water. The oily mixture of 6-, 5- (or ev. 3-) and 4-nitro isomers was hydrolysed in hydrochloric acid-ethanol solution (1:2) by boiling for 8 h. Afterwards the amine mixture was carefully steam distilled. The organic layer was dissolved in ether and dried. HCl gas was introduced and most of the 5- (or 3-) and 4-nitroamines were removed as HCl salts. The 6-nitroamine was untouched and was further purified by column chromatography (silica gel < 200 mesh ASTM pH = 7, benzene as eluent). The yield of 2-*t*-butyl-6-nitroaniline was only about 5 % (0.75 g), based on the 2-*t*-butylacetanilide. The m.p. was 63.5–64.5 °C. The compound is not described in the literature. The mass spectrum gave the molecular ion at *m/e* 194.

^{1}H NMR for 2-*t*-butyl-6-nitroaniline ($CDCl_3$): δ 7.38 (H-3, q), 6.63 (H-4, q), 8.05 (H-5, q), 1.47 [$C(CH_3)_3$, s], 6.58 (NH_2, s). $J_{3-4} = 7.4$ Hz, $J_{4-5} = 8.2$ Hz and $J_{3-5} = 1.4$ Hz.

2-t-Butyl-4-nitroaniline was separated from 2-*t*-butyl-5-nitroaniline by thin-layer chromatography (silica gel. benzene as eluent). The mass spectra gave the molecular ion for each of them at *m/e* 194.

^{1}H NMR for 2-*t*-butyl-4-nitroaniline ($CDCl_3$): δ 8.15 (H-3, d), 7.9 (H-5, q), 6.55 (H-6, d), 1.42 [$(CH_3)_3C$, s], 4.55 (NH_2, s). $J_{3-5} = 2.3$ Hz and $J_{5-6} = 8.3$ Hz.

2-Bromo-3-t-butylnitrobenzene was synthesized from 0.58 g (0.003 mol) of 2-*t*-butyl-6-nitroaniline as described above for 2-bromo-3-methylnitrobenzene. The reaction mixture was extracted with ether and then evaporated and purified by column chromatography with the same conditions as for the 2-*t*-butyl-6-nitroaniline. The yield was 0.40 g (52 %). This liquid compound is not described in the literature. The mass spectrum showed a 1:1 doublet at *m/e* 257 and 259 pointing at the desired substance.

Copper(I) chloride was purified according to Keller and Wycoff.[43]

Copper(I) catalysed replacement of bromine by chloride ion. The reactions between the halonitrobenzenes and copper(I) chloride in aqueous hydrochloric acid-acetic acid were performed in an argon atmosphere with the composition of the medium, the apparatus and the method described in Ref. 1. The withdrawn samples were adjusted to pH 7 and then extracted with ether. The ether phase was analysed on a Perkin Elmer F 11 Hot Wire Gas Chromatograph, equipped with a Varian Model 480 Electronic Digital Integrator. A 3 mm o.d. 2 m SE-30 column was used, temp. 105–150 °C, carrier gas He. Calibration curves were made from known mixtures of pure compounds: 2-bromo-3-fluoro- and 2-chloro-3-fluoronitrobenzene, 2-bromo-5-fluoro- and 2-chloro-5-fluoronitrobenzene, 2-bromo-3-methyl- and 2-chloro-3-methylnitrobenzene, 2-bromo-3-ethyl- and 2-chloro-3-ethylnitrobenzene and 2-bromo-5-methyl- and 2-chloro-5-methylnitrobenzene. All the calibration curves were straight lines with unit slope. The reaction mixtures were also analysed by NMR and IR spectroscopy (see Ref. 1).

For the 3-*t*-butylnitrobenzene compounds the calibration curve was assumed to be a straight line with unit slope.

The irradiation of 2-bromo-3-methylnitrobenzene was carried out in a photochemical reactor Rayonet RPR-100, at 350 nm, 30 °C. Otherwise the conditions were the same as described above for the exchange reactions.

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