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Nucleophilic Substitution Reaction of 2,3,5,6-Tetrachloronitrobenzene with Primary and Secondary Amines under High Pressure

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Nucleophilic substitution of 2,3,5,6-tetrachloronitrobenzene with secondary amines such as morpholine, piperidine, pyrrolidine, diethylamine, and ethylmethylamine, and primary amines such as aniline, benzylamine, butylamine, isobutylamine, *s*-butylamine, and *t*-butylamine, under high pressure of 0.6 GPa at 50 °C for 1—40 h in tetrahydrofuran gave nitro group substitution products together with ortho-mono-, meta-mono-, ortho-ortho-, and ortho-meta-dichloro substitution products. The ratio of these products depends on the bulkiness and amount of amines and the reaction conditions. The selectivity of the nitro group substitution and chlorine substitution depends mainly on the bulkiness of amines.

Nucleophilic substitution of aromatic halides with amines is usually sluggish in comparison with the reaction of aliphatic halides, and is limited to halides having strong electron-withdrawing substituents with amines of strong nucleophilicity.[1,2] In our previous papers on this work, we have reported that these S_NAr reactions of mono-, di-, and trichloronitrobenzenes with amines are effectively accelerated under high pressure, producing the corresponding *N*-alkyl nitroanilines in high yields through chlorine substitution without affording nitro group substitution products.[3] On the other hand, the reaction of pentachloronitrobenzene with secondary amines such as morpholine and pyrrolidine gave nitro group substitution products together with the expected mono-, di-, and trichloro substitution products.[4] To investigate the factors effecting on the selectivity of nitro group substitution and chlorine substitution in the S_NAr reactions of polychlorinated nitrobenzenes with amines,[5] we studied the reaction of 2,3,5,6-tetrachloronitrobenzene (**1**) with various primary and secondary amines.[6] The effects of polychlorination on the reactivity of S_NAr reaction of aryl halides were also studied.

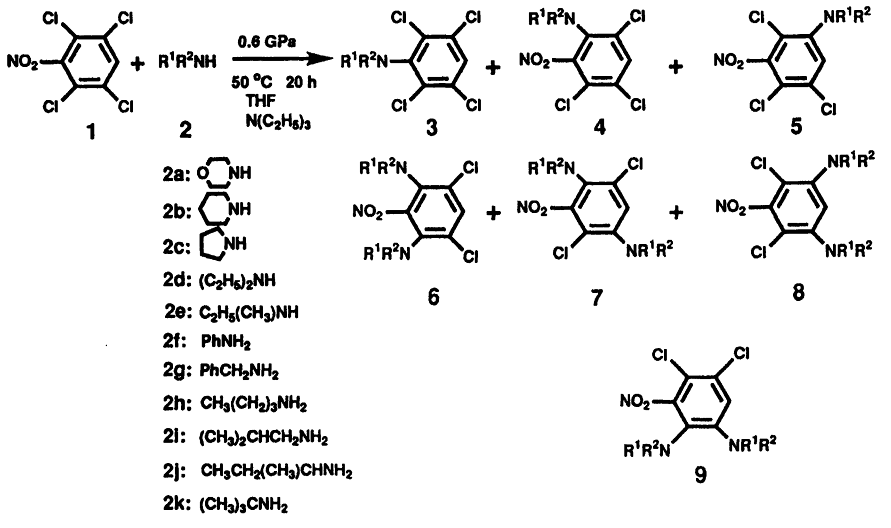
Results and Discussion

The Reaction of 2,3,5,6-Tetrachloronitrobenzene (1) with Secondary Amines. The reaction of **1** with an equimolar amount of morpholine at 0.60 GPa in tetrahydrofuran (THF) in the presence of 5.0 molar triethylamine[7] (at 50 °C, for 20 h) gave a nitro group substitution product (**3a**: 1.6%), ortho-mono- (**4a**: 30%), and meta-mono-chlorine substitution products (**5a**: 6.7%) together with recovered **1** (59%) (Scheme 1). However, when 6.0 molar morpholine was used, ortho-ortho- (**6a**: 7.9%) and ortho-meta-dichloro substitution products (**7a**: 1.2%) were obtained besides **3a** (5.0%), **4a** (65%), and **5a** (16%) (Table 1, Run 2). These products were characterized on the basis of the results of elemental analysis and spectroscopic data.

Product **3a** does not show the characteristic absorption band of the nitro group in its IR spectrum, and shows four signals of aromatic carbon at $\delta=147.28$ (C_{Ar}–N), 132.60 (*m*-C_{Ar}–Cl), 132.09 (*o*-C_{Ar}–Cl), 127.42 (C_{Ar}–H) in its ^{13}C NMR spectrum. These spectroscopic data are consistent with the structure **3a**.

The ratios of the aromatic part and morpholine part in the mono- and dichloro substitution products are easily calculated from the results of elemental analysis and the intensity ratio of the aromatic proton and methylene protons of the morpholine moiety in their ^{1}H NMR spectra (Table 2). Locations of the substitution in these products are based on the NMR measurement. The structure of the two monochloro substitution products, ortho-mono- and meta-mono-substitution products, was identified as follows. Substitution of a chlorine atom by a secondary amine usually causes a high field shift of the signal of the adjacent aromatic proton.[3] Therefore, the minor mono-substitution product which has a signal of an aromatic proton at a higher magnetic field ($\delta=7.23$) was assigned to meta-mono-substitution product **5a**, and the major one which has a signal at $\delta=7.62$ was assigned to ortho-mono-substitution product **4a**.

Of four possible isomers (2,6-diamino- **6**, 2,5-diamino- **7**, 3,5-diamino- **8**, and 2,3-diamino-substituted product **9**), the reaction of **1** with morpholine gave only two dichloro substitution products. The major disubstitution product (7.9% yield) has four aromatic carbon signals in its ^{13}C NMR spectrum (Table 2) which suggests the symmetric structure **6a** or **8a**. The low field chemical shift of aromatic proton ($\delta=7.45$) of the major product indicated the ortho disubstitution to give 2,6-disubstitution product **6a**. Six aromatic carbon signals of the minor disubstitution product (1.2% yield) suggest the possibility of asymmetric structures **7a** or **9a**. The value of chemical shift of its aromatic proton ($\delta=7.06$) is not valid to decide on structure **7a** or **9a**, because both **7a** and **9a** have two morpholino groups, one is in the meta and the other in the ortho position, which may have similar effects on the value of chemical shift of the aromatic proton. To identify the structure of the minor disubstitution product, the NOE signal was measured. Irradiation on N–CH_2 protons ($\delta=3.87$) of the morpholino group in the meta position gave an NOE effect to the aromatic proton, and to O–CH_2 protons ($\delta=3.06$) of the same morpholino group without afford-



Scheme 1.

Table 1. Reaction of 2,3,5,6-Tetrachloronitrobenzene (**1**) with Amines under High Pressure[a)]

Run	Amine (mmol)		NEt3	Yield/%[b)]						Total yield	Recovered	Ratio
			mmol	**3**	**4**	**5**	**6**	**7**	**8**	%	**1** (%)	**3**/TY
1	Morpholine	(1.0)	5.0	1.6	30.2	6.7	0	0	0	38.5	58.6	0.04
2	Morpholine	(6.0)	0	5.0	65.3	16.4	7.9	1.2	0	95.8	0	0.05
3	Piperidine	(1.0)	5.0	5.3	72.2	10.4	0	0	0	87.9	8.1	0.06
4	Piperidine	(6.0)	0	6.7	21.1	15.0	51.6	2.9	1.1	98.0	0	0.07
5	Pyrrolidine	(1.0)	5.0	38.0	42.1	8.6	0.6	0	0	89.3	1.9	0.43
6	Pyrrolidine	(6.0)	0	46.1	0	7.9	32.2	3.6	1.2	91.0	0	0.51
7	Diethylamine	(1.0)	5.0	0	7.1	0	0	0	0	7.1	87.1	0
8	Diethylamine	(6.0)	0	5.3	41.6	5.4	0	1.2	0	53.5	36.6	0.10
9	Methylethylamine	(6.0)	0	12.7	36.0	9.5	36.6	5.1	0	99.3	0	0.12
10	Aniline	(6.0)	0	0	0	0	0	0	0	0	100	0
11[c)]	Aniline	(1.0)	5.0	7.1	21.1	16.9	5.3	0	0	50.5	35.6	0.14
12	Benzylamine	(1.0)	5.0	64.7	14.3	0	0	0	0	79.0	8.0	0.82
13	Benzylamine	(6.0)	0	73.4	0	0	1.8	0	0	75.2	0	0.98
14	Butylamine	(1.0)	5.0	82.8	15.7	0	0	0	0	98.5	1.1	0.84
15	Butylamine	(6.0)	0	84.0	0	0	15.3	0	0	99.3	0	0.85
16	Isobutylamine	(1.0)	5.0	48.2	17.7	3.4	0.9	0	0	70.2	14.4	0.69
17[d)]	Isobutylamine	(6.0)	0	70.8	0	0	22.2	0	0	93.0	0	0.76
18	*s*-Butylamine	(1.0)	5.0	40.3	19.1	6.6	1.7	0	0	67.7	16.1	0.60
19[d)]	*s*-Butylamine	(6.0)	0	63.3	15.9	0	9.8	0	0	89.0	0	0.71
20[d)]	*t*-Butylamine	(1.0)	5.0	7.3	2.4	0	0	0	0	19.7	74.2	0.37
21	*t*-Butylamine	(6.0)	0	21.3	19.5	5.0	0	0	0	45.8	49.1	0.47

a) The reactions were carried out under the following conditions: 0.6 GPa, 50 °C, 20 h, in THF. b) Isolated yield by medium pressure column chromatography unless otherwise described. c) The reaction was carried out under the following conditions: 1.0 GPa, 80 °C, 50 h, in THF. d) The yields were determined by ^{1}H NMR.

ing NOE to the N–CH$_2$ of the other morpholino group. These results indicate that the two morpholino groups are not adjacent (C-2 and C-3), and that the minor product was assigned to the structure **7a**, eliminating the possibility of **9a**.

The reaction of **1** with piperidine also gave similar results affording nitro group substitution product **3b**, and chloro substitution products **4b**, **5b**, **6b**, **7b**, and **8b** in the yields shown in Table 1. The third disubstitution product obtained in this reaction was assigned to 3,5-disubstitution product **8b** on the basis of the chemical shift of the aromatic proton (δ=6.71) and four ^{13}C NMR signals of aromatic carbons.

The reaction of **1** with an equimolar amount of pyrrolidine in the presence of excess triethylamine gave nitro group substitution product **3c** in high yield (38%) along with ortho-mono- **4c** (42%), meta-mono- **5c** (8.6%), ortho-ortho-dichloro substitution product **6c** (0.6%), and recovered **1** (1.9%). The reaction with 6.0 molar pyrrolidine increased the yield of **6c** to 32% with the sacrifice of the yield of **4c**. Other disubstitution reactions at 2,5- and 3,5-positions were also observed to

Table 2. ^{1}H NMR and ^{13}C NMR Data of Reaction Products of 2,3,5,6-Tetrachloronitrobenzene (**1**) with Secondary Amines

Product	^{13}C NMR/δ (ppm)				^{1}H NMR/δ (ppm)			
	Arom-C	NCH_2	OCH_2	CH_2 or CH_3	Arom-H	NCH_2	OCH_2	CH_2 or CH_3
3a	127.42 132.09 132.60 147.28	49.47	67.51		7.43(s)	3.23(t)	3.84(t)	
4a	122.70 131.02 132.13 133.80 139.50 150.91	49.36	66.99		7.62(s)	2.85—3.73(m)		
5a	118.21 119.00 122.35 133.16 149.34 150.22	51.33	66.59		7.23(s)	3.10(t)	3.87(t)	
6a	132.26 132.87 138.89 152.90	49.58	67.37		7.45(s)	2.81—3.71(m)		
7a	117.75 122.75 134.29 135.22 148.39 152.63	49.67	66.78		7.06(s)	2.73—3.88(m)		
		51.45	67.46					
3b	126.40 131.80 132.32 149.06	50.85	24.21	26.50	7.35(s)	3.14(t)		1.65(m)
4b	122.95 129.80 132.13 133.85 141.77 150.50	50.86	32.78	26.26	7.56(s)	3.03(s,br)		1.57(m)
5b	117.09 119.02 122.40 132.82 150.25 150.84	52.59	23.79	25.82	7.17(s)	3.00(t)		1.74(m) 1.61(m)
6b	130.98 132.17 140.64 151.75	50.69	23.86	26.30	7.37(s)	2.88(s,br)		1.61(m) 1.74(m)
						3.14(s,br)		
7b	117.70 122.75 133.92 136.50 149.07 152.08	50.91	23.94	25.99	7.02(s)	2.86(s,br)		1.59(m) 1.73(m)
		52.75	26.48			3.23(s,br)		
						2.96(t)		
8b	112.60 112.88 150.68 153.20	52.70	24.02	26.00	6.71(s)	2.97(t)		1.58(m) 1.73(m)
3c	127.13 131.70 133.96 145.95	49.45	26.45		7.38(s)	3.29(m)		1.99(m)
4c	122.68 130.23 132.22 133.94 139.12 152.20	50.87	26.17		7.57(s)	3.21(m)		1.94(m)
5c	110.76 112.09 117.05 132.58 146.48 150.96	51.32	25.66		6.91(s)	3.48(m)		1.98(m)
6c	131.75 132.65 138.15 155.35	50.93	26.26		7.45(s)	3.20(m)		1.93(m)
7c	109.78 117.79 129.90 134.25 145.82 154.77	51.27	25.50	26.29	6.85(s)	3.14—3.45(m)		1.98—1.86(m)
		51.12						
8c	102.39 103.61 146.42 152.13	51.00	25.45		6.24(s)	3.42(m)		1.94(m)
3d	127.31 131.70 134.56 147.35	46.58	14.11		7.42(s)	3.22(q)		1.03(t)
4d	122.50 131.12 131.82 135.45 140.05 152.99	47.03	13.70		7.59(s)	3.12(q)		1.00(t)
5d	117.03 119.70 124.21 132.42 148.64 150.50	46.09	12.20		7.18(s)	3.18(q)		1.09(t)
7d	110.79 114.08 129.82 144.12 146.80 151.54	46.26	12.46	12.27	6.63(s)	3.26(m)		1.09—1.17(m)
		46.80				3.15(m)		
3e	127.11 131.76 133.61 148.62	48.76	13.84		7.40(s)	3.18(q)		1.07(t)
		39.65				2.84(s)		
4e	122.67 130.81 132.05 134.72 141.18 151.90	48.91	13.52		7.57(s)	3.09(q)		1.03(t)
		39.73				2.77(s)		
5e	116.50 118.06 122.29 132.65 150.27	49.73	12.40		7.17(s)	3.15(m)		1.19(t)
		39.44				2.81(s)		
6e	132.26 132.73 140.00 154.43	48.85	13.60		7.40(s)	3.08(q)		1.00(t)
		39.88				2.76(s)		
7e	116.95 122.86 134.53 135.35 149.15	49.83	13.81		7.02(s)	3.09(m)		1.19(t)
		49.10	12.54			2.78(s)		0.99(t)
		40.39				2.75(s)		
		39.68						

give **7c** and **8c**, respectively. These products were characterized in a similar manner as the reaction products of morpholine. **8c** also showed an aromatic ^{1}H NMR signal at high field of δ=6.24.

The reaction of **1** with diethylamine gave nitro group substitution product **3d** along with two mono-substitution products (**4d** and **5d**) and a trace of 2,5-disubstitution product **7d** without affording other types of disubstitution products observed in the reactions of cyclic secondary amines. The recovery of a large amount of **1**, even in the case when 6.0 molar diethylamine was used, indicates the lower reactivity of diethylamine than cyclic secondary amines described above. Ethylmethylamine is more reactive than diethylamine and gave products in high total yield without recovery of **1**. The main differences of the reactivity of ethylmethylamine from that of diethylamine is the high yields of nitro group substitution product **3e** (13%) and ortho-ortho-dichloro substitution product **6e** (37%), which are attributable to the bulkiness of amines.

To measure the reactivity and regioselectivity in the first and the second substitution steps, the reactions of **1** with 6.0 molar morpholine and pyrrolidine were traced by monitoring the reaction products by use of ^{1}H NMR measurement as shown in the Experimental part. In the reaction with morpholine, the yields of **3a**, **4a**, and **5a** increased monotonously during the initial 20 h with the monotonous decrease of starting **1** to zero recovery. After 20 h, the amount of meta-mono substitution product **5a** did not change. However, the amount of ortho-mono substitution product **4a** decreased a little with increase of the yields of disubstitution products

Table 3. ^{1}H NMR and ^{13}C NMR Data of Reaction Products of 2,3,5,6-Tetrachloronitrobenzene (**1**) with Primary Amines

Product	^{13}C NMR/δ (ppm)				^{1}H NMR/δ (ppm)				
	Arom-C	NCH$_2$	CH or CH$_2$	CH$_3$	Arom-H	NH	NCH$_2$	CH or CH$_2$	CH$_3$
3f	117.37 122.02 125.59 127.11 129.09 132.22 139.44 142.12				7.42(s) 7.26—6.73(m)	6.01(s)			
4f	118.35 123.17 124.37 128.65 129.28 129.36 132.42 132.45 141.17 146.05				7.68(s) 7.68—6.78(m)	5.92(s)			
5f	119.51 124.00 124.37 125.63 126.40 129.29 135.58 136.51 140.28 141.90				7.29(s) 7.22—6.81(m)	6.30(s)			
6f	118.07 122.69 122.72 129.18 133.44 134.33 139.91 141.26				7.60(s) 7.26—6.79(d)	6.73(s)			
3g	122.59 122.77 127.61 127.83 128.63 131.94 138.72 145.05	51.52			7.11(s) 7.34—7.22(m)		4.48(s)		
4g	122.61 123.08 124.35 127.97 128.28 129.01 131.11 136.69 137.30	49.17			7.52(s) 7.40—7.28(m)	4.55(t,br)	4.23(s)		
6g	115.77 127.92 128.82 132.79 134.85 138.20 138.68	50.94			7.39(s) 7.36—7.23(m)	4.84(t,br)	4.23(s)		
3h	121.87 122.11 131.90 145.56	47.40	32.96 19.96	13.78	7.14(s)	4.09(s,br)	3.37(t)	1.56—1.39(m)	0.94(t)
4h	121.18 122.04 124.28 130.81 136.86 138.40	43.87	32.34 19.75	13.63	7.47(s)	4.33(s,br)	3.07(t)	1.58—1.38(m)	0.93(t)
6h	113.77 132.47 133.32 139.15	46.25	32.70 19.80	13.67	7.31(s)	4.56(s,br)	3.08(t)	1.51—1.35(m)	0.91(t)
3i	121.58 121.69 131.94 145.53	55.21	29.46	20.12	7.11(s)	4.23(s,br)	3.21(d)	1.81(m)	0.98(d)
4i	121.20 122.08 124.34 130.85 136.94 138.50	51.71	29.18	19.92	7.48(s)	4.43(s,br)	2.87(d)	1.81(m)	0.96(d)
6i	113.46 132.74 139.40	54.21	29.42	20.00	7.32(s)	4.62(s,br)	2.90(d)	1.79(m)	0.93(d)
3j	122.15 122.90 131.91 144.96	53.61	30.77 20.89	10.32	7.16(s)	3.86(s,br)	3.86(m)	1.53(m) 1.13(d)	0.96(t)
4j	122.85 123.95 124.17 131.17 136.73 140.97	52.97	30.87 21.22	10.01	7.50(s)	4.00(s,br)	3.28(m)	1.46(m) 1.11(d)	0.90(t)
5j	119.95 121.94 125.33 135.23 139.12	52.86	30.95 21.28	10.01	7.03(s)	4.33(d,br)	3.29(m)	1.51(m) 1.14(d)	0.90(t)
6j	116.30 116.36 132.72 132.74 136.51 136.53 138.28	53.47 53.45	30.78 20.91 30.77 20.89	10.15 10.12	7.35(s)	4.21(s,br)	3.37(m)	1.42(m) 1.06(d)	0.89(t)
3k	125.28 129.29 131.81 145.01	57.41	31.17		7.31(s)	3.62(s,br)			1.33(s)
4k	123.63 128.55 131.40 132.08 137.01 148.69	56.77	30.71		7.62(s)	3.50(s,br)			1.22(s)

6a and **7a** (Fig. 1). This indicates that the second attack of morpholine of **4a** proceeds slowly under these reaction conditions to give **6a** and **7a**, in contrast to no attack on **5a**.

The reaction of pyrrolidine is faster than that of morpholine,$^{3)}$ and almost all **1** was consumed in the first 10 h (Fig. 2). The most interesting result in this reaction is that the high yield (45%) of nitro group substitution product **3c** was observed at the early stage of the reaction (5 h). The yield of **3c** was constant with in experimental error after 10 h. The yields of ortho-mono- **4c** became maximum at 5 h, and after that, **4c** decreased gradually with the increase of disubstitution products **6c** and **7c** until all **4c** was consumed completely in 20 h. This means that the second attack of pyrrolidine onto **4c** gives disubstitution products **6c** and **7c**. On the contrary, the decrease of the yield of **5c** is found to be slower than that of **4c**.

The Reaction of 2,3,5,6-Tetrachloronitrobenzene 1 with Primary Amines. To get more information about the regioselectivity in the S$_N$Ar reaction of **1**, the reactions with primary amines were studied. Under the same reaction conditions, aniline gave

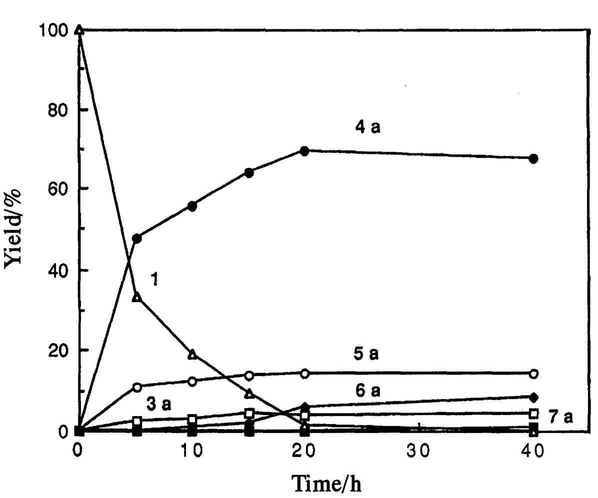


Fig. 1. Monitoring of products in the reaction of 1 with morpholine.

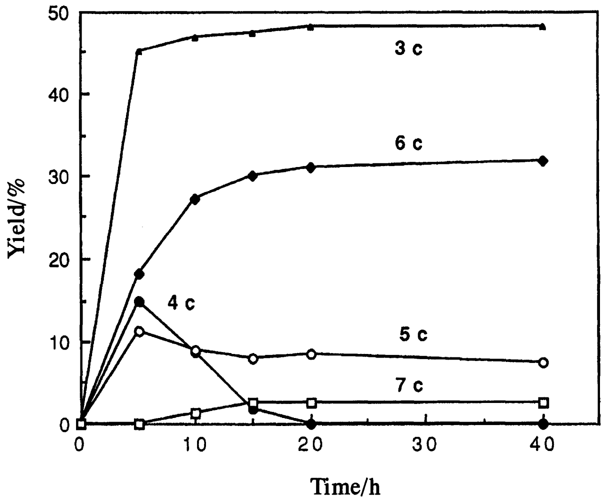


Fig. 2. Monitoring of products in the reaction of 1 with pyrrolidine.

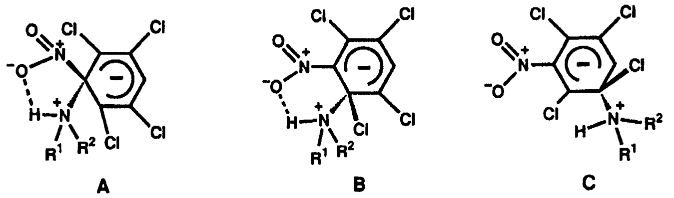


Fig. 3. Possible intermediates of nitro group (**A**), *o*- (**B**), and *m*-chlorine (**C**) substitution.

Table 4. IR Data of Reaction Products of 2,3,5,6-Tetrachloronitrobenzene (**1**) with Amines[a)]

Product	cm^{-1}
3a	2850 2828 1539 1425 1265 1158 1104 982 849 696
4a	3056 2867 1544 1437 1355 1296 1263 1145 1109 974 740
5a	2971 2861 1549 1448 1360 1247 1118 990 866 698
6a	2955 2855 1541 1448 1370 1263 1114 860 744
7a	2960 2855 1539 1448 1366 1263 1112 963
3b	2932 2847 1534 1424 1389 1046 969 699
4b	2940 2841 1534 1447 1356 1210 963 737
5b	2935 2829 1542 1447 1363 1352 1248 865
6b	2938 2827 1541 1534 1450 1371 1311 1226 856 742
7b	2930 2847 1530 1473 1461 1368 1230 953
8b	2942 2815 1581 1550 1450 1381 1218 1104 994 864
3c	2968 2841 1538 1399 1387 1044 1007 848 699
4c[b)]	2971 2870 1550 1442 1356 1235 1174 1141 873 742
5c	2979 2852 1587 1546 1380 1245 1136 747
6c	2962 2864 1550 1541 1439 1380 1134 870 773
7c	2971 2846 1592 1539 1477 1455 1382 1349 1146 987 890 747
8c	2969 2850 1577 1535 1491 1477 1384 1318 1135 884
3d[b)]	2965 2923 2850 1534 1425 1390 1376 1160 698
4d[b)]	2973 2929 2851 1550 1437 1382 1369 1342 1126 843 740
5d[b)]	2975 2933 1576 1550 1450 1374 1343 1179 1097 843 740
7d	2931 1590 1550 1462 1379 1328 1254 1113 779 665
3e	2968 2923 2850 1534 1390 1343 1159 1009 698
4e	2971 2929 1550 1442 1417 1124 740
5e	2966 2856 1576 1544 1472 1450 1368 1183 1020 862
6e	2970 2930 1544 1449 1381 1196 833 743
7e	2972 2935 2857 1549 1482 1460 1366 1176 1019 886 743
3f	3377 1602 1551 1540 1496 1444 1421 1405 1368 1222 1157 760 698
4f	3383 1575 1550 1498 1448 1348 742 692
5f	3381 1560 1530 1499 1442 1414 1360 1342 1270 762 694
6f	3401 1526 1496 1478 1449 1263 746
3g[b)]	3389 3028 1546 1492 1408 1383 1061 698
6g	3393 3028 2917 1580 1528 1460 1350 1221 699
3h[b)]	3390 2958 2935 1543 1489 1419 1387 1062 712
4h	3406 2949 1592 1540 1498 1362
6h[b)]	3402 2959 2929 1588 1534 1490 1363
3i[b)]	3401 2971 2961 1550 1418 1379
4i[b)]	3405 2957 2926 1590 1535 1496 1440 1358
6i[b)]	3401 2957 2926 2870 1582 1533 1497 1465 1368 1224
3j[b)]	3370 2964 2930 2873 1545 1488 1405 1381
4j[b)]	3379 2966 2927 2876 1584 1540 1450 1363
5j[b)]	3375 2966 2925 2851 1568 1534 1419 1362
6j[b)]	3372 2967 2924 2853 1575 1534 1482 1451 1352
3k[b)]	3374 2967 2870 1589 1540 1451 1389 1362 1191 986
4k[b)]	3376 2969 1549 1435 1395

a) Measured in KBr pellet unless otherwise described. b) Measured in neat liquid film.

Table 5. Melting Points and Results of Elemental Analysis of the Products

Product	Mp	Found/%			Calcd/%			Molecular formula
	θ_m/°C	C	H	N	C	H	N	
3a	70.4—71.3	39.81	3.03	4.65	39.89	2.99	4.65	$C_{10}H_9NOCl_4$
4a	123.2—123.9	38.46	2.94	8.98	38.55	2.91	8.99	$C_{10}H_9N_2O_3Cl_3$
5a	131.0—132.2	38.74	3.00	8.92	38.55	2.91	8.99	$C_{10}H_9N_2O_3Cl_3$
6a	220.0—221.0	46.87	4.77	11.58	46.42	4.73	11.60	$C_{14}H_{17}N_3O_4Cl_2$
7a	223.1—224.3	46.33	4.71	11.49	46.42	4.73	11.60	$C_{14}H_{17}N_3O_4Cl_2$
3b	Oil	44.40	3.74	4.69	44.18	3.68	4.69	$C_{11}H_{11}NCl_4$
4b	76.2—77.9	42.61	3.59	9.07	42.67	3.56	9.05	$C_{11}H_{11}N_2O_2Cl_3$
5b	80.5—82.6	42.76	3.60	9.09	42.67	3.56	9.05	$C_{11}H_{11}N_2O_2Cl_3$
6b	160.5—162.2	53.52	5.83	11.71	53.65	5.89	11.74	$C_{16}H_{21}N_3O_2Cl_2$
7b	162.5—163.4	53.74	5.86	11.78	53.65	5.89	11.74	$C_{16}H_{21}N_3O_2Cl_2$
8b	173.9—175.2	53.67	5.83	11.68	53.65	5.89	11.74	$C_{16}H_{21}N_3O_2Cl_2$
3c	71.3—72.6	42.18	3.23	4.86	42.13	3.16	4.90	$C_{10}H_9NCl_4$
4c	Oil	40.82	3.17	9.43	40.64	3.07	9.48	$C_{10}H_9N_2O_2Cl_3$
5c	138.1—139.5	40.90	3.16	9.45	40.64	3.07	9.48	$C_{10}H_9N_2O_2Cl_3$
6c	118.0—119.2	51.13	5.22	12.74	50.92	5.19	12.72	$C_{14}H_{17}N_3O_2Cl_2$
7c	142.0—144.0	50.98	5.21	12.60	50.92	5.19	12.72	$C_{14}H_{17}N_3O_2Cl_2$
8c	179.5—181.0	50.95	5.20	12.66	50.92	5.19	12.72	$C_{14}H_{17}N_3O_2Cl_2$
4d	Oil	HRMS	295.9884			295.9885		$C_{10}H_{11}N_2O_2Cl_3$
5d	Oil	HRMS	295.9900			295.9885		$C_{10}H_{11}N_2O_2Cl_3$
4e	Oil	38.27	3.26	9.86	38.12	3.20	9.88	$C_9H_9N_2O_2Cl_3$
5e	96.5—98.2	38.00	3.24	9.90	38.12	3.20	9.88	$C_9H_9N_2O_2Cl_3$
6e	103.2—104.5	47.13	5.56	13.68	47.07	5.60	13.72	$C_{12}H_{17}N_3O_2Cl_2$
7e	Oil	47.07	5.53	13.77	47.07	5.60	13.72	$C_{12}H_{17}N_3O_2Cl_2$
3f	102.5—103.7	47.04	2.41	4.59	46.90	2.28	4.56	$C_{12}H_7NCl_4$
4f	121.8—123.4	45.42	2.34	8.83	45.38	2.21	8.82	$C_{12}H_7N_2O_2Cl_3$
5f	102.9—104.5	45.42	2.35	8.81	45.38	2.21	8.82	$C_{12}H_7N_2O_2Cl_3$
6f	160.2—162.0	58.32	3.67	11.17	57.78	3.48	11.23	$C_{18}H_{13}N_3O_2Cl_2$
3g	50.5—51.8	48.68	2.85	4.37	48.63	2.81	4.36	$C_{13}H_9NCl_4$
6g	Oil	HRMS	401.0698			401.0706		$C_{20}H_{17}N_3O_2Cl_2$
3h	25.6—26.2	42.00	3.87	4.89	41.85	3.86	4.88	$C_{10}H_{11}NCl_4$
4h	43.7—44.5	40.32	3.53	9.42	40.36	3.70	9.41	$C_{10}H_{11}N_2O_2Cl_3$
6h	Oil	HRMS	333.0993			333.1010		$C_{14}H_{21}N_3O_2Cl_2$
3i	Oil	42.00	3.90	5.04	41.85	3.86	4.88	$C_{10}H_{11}NCl_4$
4i	Oil	HRMS	295.9878			295.9886		$C_{10}H_{11}N_2O_2Cl_3$
6i	Oil	50.85	6.39	12.28	50.31	6.33	12.75	$C_{14}H_{21}N_3O_2Cl_2$
3j	Oil	HRMS	284.9641			284.9648		$C_{10}H_{11}NCl_4$
4j	Oil	HRMS	295.9879			295.9886		$C_{10}H_{11}N_2O_2Cl_3$
5j	Oil	40.08	3.62	9.05	40.36	3.70	9.41	$C_{10}H_{11}N_2O_2Cl_3$
6j	Oil	50.70	6.34	12.37	50.31	6.33	12.57	$C_{14}H_{21}N_3O_2Cl_2$
3k	Oil	42.01	3.87	4.91	41.85	3.86	4.88	$C_{10}H_{11}NCl_4$
4k	Oil	40.31	3.69	9.35	40.36	3.70	9.41	$C_{10}H_{11}N_2O_2Cl_3$

no product; all **1** was recovered. The forced reaction conditions (1.0 GPa, 80 °C, 50 h) gave **3f**, **4f**, **5f**, and **6f** in total yield of 51% (Table 1, Run 11). On the contrary, aliphatic primary amines such as benzylamine and butylamines show high reactivity toward **1** affording **3**, **4**, **5**, and **6**, in good yields. Benzylamine gave the nitro group substitution product **3g** in high yield (65—73%). There are two possible explanations of the differences in the reactivity and selectivity between aniline and benzylamine. One is the nucleophilicity, which may be related to the basicity of aniline ($\mathrm{p}K_\mathrm{b}=9.40$) and benzylamine ($\mathrm{p}K_\mathrm{b}=4.40$), the other is the bulkiness of amines. To decide on the validity of these two possibilities, we studied the reaction of **1** with butylamines which have similar basicity ($\mathrm{p}K_\mathrm{b}=3.40$, 3.51, 3.36, and 3.47) and different bulkiness. A decrease in the total yield of the reaction products was observed in the reaction of *s*-butylamine and *t*-butylamine in these reactions (Table 1, Runs 14—21). The selectivity of nitro group substitution decreases largely according to the increase of bulkiness of the amine, and the ratio of the yield of **3** to the total yield of products, ratio **3**/TY, changes: 0.84 for butylamine and 0.37 for *t*-butylamine.

Discussion

Although the nucleofugicity of the nitro group is larger than chlorine in the usual $\mathrm{S_NAr}$ reaction,[8,9] no nitro group substitution was observed in the high pressure $\mathrm{S_NAr}$ reaction of mono-, di-, and trichloronitrobenzenes with amines.[3] However, the nitro group substitution was observed in the reactions of pentachloronitrobenzene (**10**),[4] 2,3,5,6-tetrachloronitrobenzene (**1**),[6] 3, 4,5,6-tetrachloro-1,2-dinitrobenzene,[5] and 2,3,5,6-tetrachloro-1,4-dinitrobenzene[10] with amines. The selectivity of nitro group substitution, ratio **3**/TY, depends on the structure of the amines. For example, the values for the reaction of morpholine with **1** and **10** are 0.04 and 0.03,[4] respectively. On the other hand, the value for pyrrolidine with **1** and **10** are 0.43 and 0.20.[4] Piperidine shows similar tendency to morpholine. The difference of the regioselectivity between morpholine and pyrrolidine is explained by the bulkiness of the amine, because the nucleophilicity of these amines does not show a big difference. Similar effects of bulkiness of amines on the regioselectivity were observed in the reactions of **1** with various butylamines, and also with diethylamine and ethylmethylamine.

The initial $\mathrm{S_NAr}$ reaction products **3**, **4**, and **5** may be formed through the Meisenheimer type intermediates **A**, **B**, and **C**, respectively.[11] In the intermediates **A** and **B**, the intramolecular hydrogen bonding is possible between the amine hydrogen and the oxygen atom of the nitro group as shown in Fig. 3. The CPK model inspection of the intermediates **A** and **B** showed that destabilization caused by the bulkiness of R^1 and/or R^2 of amine affect the intermediate **A** more than **B**. This may explain the regioselectivity described above.

The meta-chlorine substitution has not been observed in the reactions of mono-, di-, and trichloronitrobenzenes with various primary and secondary amines.[3] Therefore, the interesting results of the meta-chloro substitution found in this reaction of **1** seems to be attributed to the increase of the $\mathrm{S_NAr}$ reactivity of **1** due to its polychlorinated structure. In this context, the fact that meta-chloro substitution was not observed in the reaction of pentachloronitrobenzene (**10**)[4] may be explained by the decrease of the reactivity of meta-position by its steric crowding in **10**.

Experimental

General. Melting points were measured with a Yanagimoto Melting Point Apparatus and are not corrected. IR spectra were recorded on a Perkin–Elmer model 983. ^{1}H NMR and ^{13}C NMR spectra were measured on a JEOL EX-270 in a $\mathrm{CDCl_3}$ solution using TMS as an internal standard. Mass spectra were measured with a JEOL JMS-DX303 spectrometer.

Materials. Commercial reagent of 2,3,5,6-tetrachloronitrobenzene was used after purification by recrystallization. THF was purified by distillation after reflux over $\mathrm{LiAlH_4}$, and stored with molecular sieves type 4A under a nitrogen atmosphere. Amines were purified by distillation under a nitrogen atmosphere after appropriate drying procedure.

General Procedure for the $\mathrm{S_NAr}$ Reaction of 1 with Amines. A THF solution (5 cm^3) of **1** (1.0 mmol) and amine (1.0 or 6.0 mmol) with or without 5.0 mmol of triethylamine was treated with high pressure in a Teflon capsule using a Hikari Kouatsu High Pressure Apparatus[12] under the reaction conditions cited in Table 1. Products were characterized on the basis of ^{1}H NMR (Tables 2 and 3), ^{13}C NMR (Tables 2 and 3), IR (Table 4), and elemental analysis (Table 5) after separation by medium pressure column chromatography (silica gel/hexane–ethyl acetate) and recrystallization from benzene–hexane.

Measurement of Product Ratio by ^{1}H NMR. Insoluble matters precipitated in the reaction mixture were removed by filtration then rinsed with small amount of toluene. When the amine salts were difficult to filter out, they were removed by treatment of the reaction mixture with short column of silica gel (eluent: ethyl acetate–hexane). After evaporation of THF, toluene, and unreacted amine to dryness under reduced pressure, the total weight of the residue was weighed. The molar ratio of the products was calculated by the integration of ^{1}H NMR signals of their singlet signals of aromatic-H which appear in the region of 6.50—7.74 ppm as shown in Table 2. The amount of each product was calculated by the molar ratio and total weight of the products.

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