Substitution Reactions of Hexachlorobenzene

ALBERT L. ROCKLIN

It is postulated that the inductive effect of the chlorine atoms should render hexachlorobenzene susceptible to nucleophilic attack, and it has been found that it does react easily with nucleophilic reagents.

Reaction rates in pyridine are much faster than in other solvents.

The moderate reactivity of hexachlorobenzene has not been readily apparent because of its poor compatibility with common solvents and reagents. Some reagents are precluded from reacting because of unfavorable steric factors.

Examination of the literature on hexachlorobenzene gives the impression that its behavior is quite erratic. Frequently it has appeared to be completely inert, as shown by its failure to react with the Grignard reagent[1] or by its resistance to attack by molten sodium hydroxide and other corrosive or reactive materials. At other times, it has yielded to attack by highly reactive reagents, but only under conditions so drastic that ordinary organic molecules would have been completely shattered in the process. A good illustration of this is its smooth reaction with vigorous fluorinating agents, [2-11] and this appeared to support the opinion that it was indeed an unreactive compound. On the other hand, there are several known reactions which do proceed smoothly under conditions that are not at all drastic. For example, it can be hydrolyzed to pentachlorophenol in methanolic[12] or in a tertiary alcoholic[13] sodium hydroxide solution at 130°, while in methanolic sodium sulphide or bisulphide there is produced pentachlorothiophenol.[14] These reactions can be modified to produce ethers[15,16] and

thioethers,[14] all under easily controllable relatively mild conditions.

It is the purpose of this paper to show that hexachlorobenzene is a moderately reactive compound, and that its behavior can be accounted for by well established principles.

Without attempting to formulate the detailed mechanism, it should be possible to predict some of the reactions of hexachlorobenzene (I) by considering the charge distribution in its molecule.

I   II
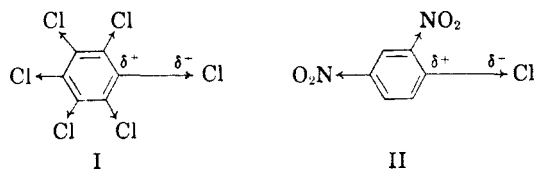
The chlorine atoms exert their full inductive effect on the ring carbons to leave them positively charged.[17] In this respect, it resembles 2,4-dinitrochlorobenzene (II), studied by Bunnett and Davis,[18] for here too is a molecule whose ring is left positively charged because of the strong electron-withdrawing groups attached to it. Since II is highly susceptible to attack by nucleophilic reagents, it can be expected that I would react in a similar manner, but would be less reactive than II because of the smaller electron-withdrawing effect of the chlorine atoms compared with the nitro groups.[19] For the same reason, it should be resistant to attack by electrophilic reagents. Therefore, it is to be expected that it would appear inert when subjected to nitration, Friedel-Crafts or sulfonation type reagents, and that when conditions are made drastic enough to bring about some sort of reaction with them, it is not one of substitution.

However, the general experience has been that the reactivity of hexachlorobenzene was not at all obvious. This can be ascribed to the difficulty in readily attaining the conditions necessary for reaction. For example, hexachlorobenzene does not react

(1) Durand and Wai-Hsun, *Compt. rend.*, **191**, 1460 (1930).

(2) Bigelow and Pearson, *J. Am. Chem. Soc.*, **56**, 2773 (1934).

(3) Fukuhara and Bigelow, *J. Am. Chem. Soc.*, **60**, 427 (1938).

(4) McBee, Lindgren, and Ligett, *Ind. Eng. Chem.*, **39**, 378 (1947).

(5) Ligett, McBee, and Lindgren, U.S. Patent 2,432,997 (1947) [*Chem. Abstr.*, **42**, 2618 (1948)].

(6) McBee, Wiseman, and Bachman, *Ind. Eng. Chem.*, **39**, 415 (1947).

(7) McBee, Lindgren, and Ligett, U.S. Patent 2,489,969 (1949) [*Chem. Abstr.*, **44**, 2019 (1950)].

(8) Ligett, McBee, and Lindgren, U.S. Patent 2,461,554 (1949) [*Chem. Abstr.*, **43**, 3845 (1949)].

(9) Lindgren and McBee, U.S. Patent 2,480,081 (1949) [*Chem. Abstr.*, **44**, 2020 (1950)].

(10) Ligett, McBee, and Lindgren, U.S. Patent 2,509,156 (1950) [*Chem. Abstr.*, **44**, 7872 (1950)].

(11) McBee, Robb, and Ligett, U.S. Patent 2,493,007 (1950) [*Chem. Abstr.*, **44**, 5375 (1950)].

(12) Smith and Livak, U.S. Patent 2,107,650 (1938) [*Chem. Abstr.*, **32**, 2548 (1938)].

(13) Bartlett, U.S. Patent 2,644,015 (1953) [*Chem. Abstr.*, **48**, 5216 (1954)].

(14) Vollmann and Giltges, U.S. Office of Technical Services, Report PB 103755.

(15) Van der Linden, *Rec. trav. chim.*, **57**, 781 (1938).

(16) Schaeffer, Blaich, and Churchill, *J. Org. Chem.*, **19**, 1646 (1954).

(17) Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, 1953.

(18) Bunnett and Davis, *J. Am. Chem. Soc.*, **76**, 3011 (1954) [See also Bunnett and Zahler, *Chem. Revs.*, **49**, 273 (1951)].

(19) Sanderson, *Science*, **122**, 598 (1955).

with sodium methoxide in boiling methanol, but it does react to form pentachloroanisole if the temperature of the system is raised to 120°. This is not a very high temperature, yet this set of conditions cannot be employed except in pressure equipment. Again, one would be led to believe that it does not react easily with methylamine, for no detectable reaction takes place when this amine is bubbled through cold or hot solutions of it in various solvents, or even at 310° when passed through boiling hexachlorobenzene itself. Yet complete reaction occurs in liquid methylamine in a closed vessel at 150°. Despite the mild conditions, the probability of discovering these reactions is much smaller than if they took place at atmospheric pressure.

Another aspect of this "inconvenience factor" is the remarkably low solubility of hexachlorobenzene in most of the common organic solvents. Its room temperature solubility is less than one percent in alcohol, diethyl ether, acetone, and dimethylformamide. Since it is customary to study substitution reactions in solution, it can be seen how poor compatibility could obscure its reactivity and discourage further investigation.

In a study carried out in this laboratory, it has been found that when the obstacles described above are circumvented, hexachlorobenzene does indeed react with nucleophilic reagents as predicted. These reactions are listed in Table I. The first three [14-16] are previously known reactions, but their yields and rates have been greatly improved. The last three reactions are entirely new. In general, they proceed smoothly and rapidly with very little by-product formation, sometimes taking only a minute or two to go to completion.

TABLE I
TYPICAL SUBSTITUTION REACTIONS OF HEXACHLOROBENZENE

1.	$C_6Cl_6 + OR^-$	$\longrightarrow C_6Cl_5OR + Cl^-$
2.	$C_6Cl_6 + SR^-$	$\longrightarrow C_6Cl_5SR + Cl^-$
3.	$C_6Cl_6 + SH^-$	$\longrightarrow C_6Cl_5SH + Cl^-$
4.	$C_6Cl_6 + NH_3$	$\longrightarrow C_6Cl_5NH_2 + HCl$
5.	$C_6Cl_6 + RNH_2$	$\longrightarrow C_6Cl_5NHR + HCl$
6.	$C_6Cl_6 + R_1R_2NH$	$\longrightarrow C_6Cl_5NR_1R_2 + HCl$

During the course of these studies, it was found that pyridine was an unusual solvent, for reaction rates in it were much faster than in other solvents. Where it had taken perhaps an hour or more for reaction with an alcoholate in its corresponding alcohol as solvent, the change to pyridine as solvent shortened this reaction time to a few minutes. Thus, pentachloroanisole can be made in one minute by adding a sodium methoxide (or hydroxide) solution in methanol to a boiling solution of hexachlorobenzene in pyridine. Reactions 2 and 3, in Table I, are affected in a similar manner by pyridine. A similar effect is noticed with substituted pyridines such as picoline and lutidine. A notable exception is 2,6-lutidine which, though

as good a solvent as the other pyridines, differs from them by its failure to exhibit their characteristic effect on the reaction rate.

From this behavior it can be reasoned that the action of the pyridines is catalytic, with this unique property attributable to the hetero nitrogen atom. The exceptional behavior of 2,6-lutidine further supports this proposal, for it has been shown by Brown and co-workers[20,21] that in this compound the nitrogen atom is blocked by the two ortho methyl groups, and hence it would not be able to get close enough to the hexachlorobenzene molecule to have as much effect on it as the other pyridines do. A study of the mechanism of this action would be a profitable undertaking.

The action of the lutidines is illustrative of the manner in which steric factors can prevent reaction from taking place between hexachlorobenzene and some nucleophilic reagents of known high activity. According to Duchesne and Monfils,[22] the quadrupole spectrum of hexachlorobenzene shows the chlorine atoms to be bent away from the plane of the ring, alternately at angles of 25°. Therefore, the vulnerable side of each ring carbon is partially shielded from attack by the two ortho chlorine atoms which protrude forward in the direction from which attack takes place. This limits reaction to those reagents of suitable geometry. So it is seen that most primary amines react fairly quickly because here the attacking amino groups are well exposed and can get by the ortho chlorines with little difficulty. Dimethylamine as well can react quickly because its molecule is a small one. Here reaction is complete in less than half an hour at 150°. But dipentylamine is fairly large and bulky, and so it is not unexpected to find only a few percent reaction even after 18 hours at 175°.

EXPERIMENTAL

Pentachlorophenyl isopropyl ether. Hexachlorobenzene (50 g., 0.175 mole) and solid sodium hydroxide, assay 97% (8.0 g., 0.194 mole) were refluxed with 500 ml. of isopropyl alcohol for 28 hours, then cooled to room temperature and filtered to remove 15.6 g. of unreacted material. The filtrate was boiled down to 150 ml. then, while still hot, diluted with water to 500 ml. and the oily organic phase was allowed to coalesce. After solidification, it was lifted out and washed by melting under hot water. The product (34.2 g., 92%) melted 54–55.5°. (Literature[23] 44.5°).

Anal. Calc'd for $C_9H_7Cl_5O$: C, 35.1; H, 4.41; Cl, 57.5. Found: C, 35.0; H, 4.5; Cl, 57.7.

Pentachloroanisole. Solid sodium hydroxide, assay 97% (4.0 g., 0.097 mole) was dissolved in 25 ml. of methanol at 50° and then added quickly, with good stirring, to a gently boiling solution of hexachlorobenzene (25 g., 0.088 mole) in

(20) Brown and Cahn, *J. Am. Chem. Soc.*, 77, 1715 (1955).

(21) Brown and Mihm, *J. Am. Chem. Soc.*, 77, 1723 (1955).

(22) Duchesne and Monfils, *J. Chem. Phys.*, 22, 562 (1954).

(23) Felton and McLaughlin, *J. Org. Chem.*, 12, 298 (1947).

100 ml. of pyridine. After one minute, the mixture was cooled to room temperature and filtered to remove sodium chloride. The product (23.3 g., 95%), m.p. 108–110° (Literature[15] 108–109°), was recovered by filtration from the pyridine filtrate that had been diluted with ice-water to 500 ml. Then it was washed with dilute acid to remove traces of pyridine.

Anal. Calc'd for $C_7H_3Cl_5O$: C, 30.0; H, 1.07; Cl, 63.4. Found: C, 30.0; H, 0.95; Cl, 63.4.

The procedure for carrying out the reaction with the same materials, but in the absence of pyridine, is as follows: Solid sodium hydroxide (0.046 g., 1.11×10^{-3} mole), hexachlorobenzene (0.30 g., 1.05×10^{-3} mole), and about 1.2 ml. of methanol were heated to 120° for one hour in a rotating stainless steel bomb of 1.75 ml. capacity. The contents were diluted with water to 10 ml. and filtered. The washed and dried residue, weighing 0.23 g. was shown by infrared analysis to be about one-third pentachloroanisole and two-thirds unreacted hexachlorobenzene.

Thioethers. Reaction with mercaptides takes place readily in pyridine. The procedure is the same as that described above for the preparation of an ether except that a mercaptan is used instead of an alcohol. Nevertheless, it is much more convenient to prepare thioethers from sodium pentachlorothiophenoxide and alkyl halides by the Williamson synthesis.

Pentachlorothiophenol. A warm solution of 97% "crystal" sodium hydroxide (63.7 g., 1.54 mole) in 200 ml. of ethylene glycol was saturated with hydrogen sulfide and added, with good stirring, over a four-minute period, to a boiling solution of hexachlorobenzene (200 g., 0.702 mole) in 800 ml. of pyridine. The solution was boiled another two minutes and then diluted with water to 3 liters. Unreacted hexachlorobenzene (9.4 g.) was removed by filtration. Slow acidification of the filtrate to pH 2 precipitated crystalline pentachlorothiophenol (180 g., 95.5%) which was recovered by filtration, then washed with water. Melting point 242–244° (Literature[14] 242°).

Anal. Calc'd for C_6HCl_5S: C, 25.5; H, 0.356; Cl, 62.8; S, 11.35; Mol. wt., 282.5. Found: C, 25.5; H, 0.4; Cl, 62.7; S, 11.2; Equiv. wt. (by silver electrode titration), 281.0.

Pentachloroaniline. Hexachlorobenzene (100 g., 0.351 mole) and 250 ml. of 28% aqueous ammonium hydroxide were heated to 250° for one hour in a one-liter stainless steel rocking Parr bomb. The aqueous phase was poured off and

the residue washed with water to remove ammonium chloride. The dried product was leached with 500 ml. of 98% sulfuric acid and filtered to remove 8 g. of unreacted hexachlorobenzene. Pentachloroaniline, m.p. 230–232° (81.3 g., 95%) was regenerated by diluting the filtrate to 2 liters with ice and water. A portion recrystallized from isoöctane melted at 233.5–234.0° (Rept'd in Beilstein, m.p. 232°).

Anal. Calc'd for $C_6H_2Cl_5N$: C, 27.15; H, 0.76; Cl, 66.8; N, 5.28. Found: C, 27.2; H, 0.80; Cl, 66.9; N, 3.9. (The high stability of these compounds makes it difficult to obtain accurate nitrogen determinations).

N-Pentachlorophenyl-ethylenediamine. Hexachlorobenzene (100 g., 0.351 mole) was dissolved over a 30-minute period in 800 ml. of boiling anhydrous ethylenediamine. The clear solution was boiled another 15 minutes, then cooled to about 40° and diluted with water and ice to 4 liters. The product, N-pentachlorophenyl-ethylenediamine, (103 g., 95%) m.p. 92–93°, was recovered by filtration.

Anal. Calc'd for $C_8H_7Cl_5N_2$: C, 31.1; H, 2.28; Cl, 57.7; N, 9.08. Found: C, 31.0; H, 2.4; Cl, 57.6; N, 7.8.

N,N-Dimethyl-pentachloroaniline. Hexachlorobenzene (50 g., 0.175 mole) and 250 ml. of liquid dimethylamine were heated to about 160° for one-half hour in a one-liter stainless steel rocking Parr bomb. The unreacted dimethylamine was evaporated off and the residue was washed with dilute hydrochloric acid and water. Recrystallization from methanol gave N,N-dimethyl-pentachloroaniline (35.7 g., 69%), m.p. 54–55.5°.

Anal. Calc'd for $C_8H_6Cl_5N$: C, 32.74; H, 2.06; Cl, 60.4; N, 4.77. Found: C, 32.7; H, 2.2; Cl, 60.2; N, 3.4.

N-Methyl-pentachloroaniline. Hexachlorobenzene (50 g., 0.175 mole) and 250 ml. of liquid methylamine (at Dry Ice temperature) were charged into a cooled one-liter stainless steel Parr bomb, then heated, with rocking, to 150° for 45 minutes. The unreacted methylamine was evaporated off and the residue was washed with water. Recrystallization from methanol gave N-methyl-pentachloroaniline (36.2 g., 74%), m.p. 94–97°. A sample recrystallized from isobutyl alcohol melted at 100–101°.

Anal. Calc'd for $C_7H_4Cl_5N$: C, 30.1; H, 1.43; Cl, 63.4; N, 5.02. Found: C, 30.4; H, 1.7; Cl, 63.1; N, 4.0.

PITTSBURG, CALIFORNIA