3-Chlorophthalic Anhydride through Chlorination of Phthalic Anhydride

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Monochlorination of molten phthalic anhydride in the presence of ferric chloride proceeds with only a small preference (55:45) for 4-chlorophthalic anhydride over 3-chlorophthalic anhydride. Under the same conditions both monochlorophthalic anhydrides are chlorinated at rates comparable to that of phthalic anhydride itself. When 1 mol of chlorine is taken up by 1 mol of phthalic anhydride, a mixture of starting material and mono- and dichlorophthalic anhydrides is obtained together with traces of the more highly chlorinated phthalic anhydrides. Distillative separation of 3-chlorophthalic anhydride from the lower boiling 4-chlorophthalic anhydride can be readily achieved on a moderately efficient column. Convenient preparation of pure 3-chlorophthalic anhydride through distillation of chlorinated phthalic anhydride mixtures is impeded by the nearly identical boiling points of 3-chlorophthalic anhydride and 4,5-dichlorophthalic anhydride. The latter is formed to the extent of one-sixth of the dichlorophthalic anhydride fraction of the chlorinated mixtures.

Although Lewis acid catalyzed chlorination of phthalic anhydride (PAA) was reported in 1909[1] and has been extensively studied in the years since then,[2] isolation or identification of 3-chlorophthalic anhydride (3-ClPAA) as a product of the reaction has never been made. Instead, 3-ClPAA has most commonly been prepared from the corresponding nitrophthalic anhydride (3-NO_2PAA) by a high temperature (230–250 °C) ipso displacement reaction.[3] The 3-NO_2PAA, in turn, is usually prepared in modest (25–29%) overall yield by nitration of PAA, fractional crystallization of the mixed mononitrophthalic acids (formed in ~1:1 ratio), and dehydration of the separated 3-nitrophthalic acid.[4]

We were interested in obtaining quantities of 3-ClPAA for use as an intermediate in a heterocyclic synthesis and became curious as to why such a round-about method is employed for its preparation. While the literature indicates that chlorination of phthalate with sodium hypochlorite gives as much as 90% of 4-ClPAA,[5] under typical electrophilic substitution conditions the ratio of monochlorination products of PAA should be similar to that of its nitration products. Indeed, the reported[6] isolation of a fair (25%) yield of 3,6-diClPAA after more extensive chlorination of PAA in the presence of Lewis acid catalysts infers that substantial amounts of 3-ClPAA are formed since rearrangement does not occur under these conditions (vide supra).

The isomer ratio of monochlorinated products of PAA is also of theoretical interest. Electrophilic chlorinations are known to involve complexation of the aromatic substrate as the donor with the electrophile as the acceptor.[7] There are few studies of such reactions where the aromatic substrate is multiply substituted with electron-withdrawing groups making it a poorer donor. Hückel molecular orbital calculations indicate that the anhydride function will have little effect on the degenerate highest filled donor molecular orbitals of the benzene ring in PAA. Thus, little positional selectivity to electrophilic attack is anticipated. Neither the "frontier electron" method nor the "Wheland intermediate" methods of analysis of the molecular orbitals[8] of PAA suggest that its electrophilic 4 substitution should predominate over its 3 substitution. Although such conjecture is suggestive, the necessary detailed experimental product analysis for this reaction has, until now, not been available.

Results and Discussion

Product Distribution. An initial exploratory investigation indicated that molten PAA at 220–230 °C is not chlorinated either neat or in the presence of catalytic quantities of nickel acetylacetonate, cupric chloride or acetate, or aluminum chloride. In the presence of mercuric chloride, only traces of 3-ClPAA and 4-ClPAA could be detected (in about equivalent amounts by GLC) after 8 h of chlorination. With several strong Lewis acids such as $MoCl_5$, $SbCl_5$, and $FeCl_3$, PAA chlorination occurred at a substantial rate. Thus, with 1 mol of PAA and 0.1 mol of $FeCl_3$ present at 220 °C after 5 and 10 h of chlorination, 56 and 92%, respectively, of the PAA had been consumed (by GLC analysis). Based on GLC analysis calibrated with authentic samples, the reaction product after 5 h of chlorination appeared to be about 25% of 4-ClPAA, 23% of 3-ClPAA, and ~4% each of two materials with longer retention times, presumably diClPAA's.

At temperatures below about 220–230 °C, the rate of PAA chlorination slowed markedly, almost completely stopping by 200 °C. Temperatures much higher than about 240 °C, desirable for more rapid chlorination, could not be effectively employed in systems open to the atmosphere because of extensive PAA sublimation. Chlorination proceeded effectively with a ferric chloride molar concentration at 1% that of the PAA, but became very slow at 0.1%. Similar patterns of conversion of PAA to chlorinated products were found in all cases. The results consistently indicated that the catalyzed monochlorination proceeds with only a small preference (ca. 55:45) for 4-ClPAA over 3-ClPAA formation.

Monitoring the composition of the mixture through GLC analysis of samples withdrawn as the chlorination proceeded showed that both monochloro PAA's steadily increased in concentration until about one-half the PAA had been consumed. Further chlorination had the effect of increasing the proportion of compounds with longer GLC retention times, presumably polychloro PAA's, at the expense of PAA with little change occurring in the monochloro PAA concentration. As chlorination continued and the PAA became almost completely consumed, the compounds with longer GLC retention times continued to increase in relative concentration at the expense of the monochloro PAA's. These results are consistent with chlorination of both monochloro PAA's proceeding at rates comparable to chlorination of PAA under the same conditions. Thus, while a chlorine substituent is known to have a moderately deactivating effect on most electrophilic aromatic substitutions,[7] its added effect on the rate of chlorination of the highly deactivated PAA system under the relatively severe conditions required is negligible. Examination of the initial data obtained suggested that 3-ClPAA might be chlorinated less rapidly than 4-ClPAA since it appeared to be consumed more slowly during the latter stages of the reaction. Full identification of the products showed this *not* to be the case. Authentic samples of 3,6-, and 4,5-diClPAA's were obtained, and 3,4-diClPAA was identified in the mixture by its characteristic proton NMR AB quartet (cf. Experimental Section). Through GLC analysis it was established that the first of the two longer retention time materials is 3,4-diClPAA and the second 3,6-diClPAA. With the nonpolar

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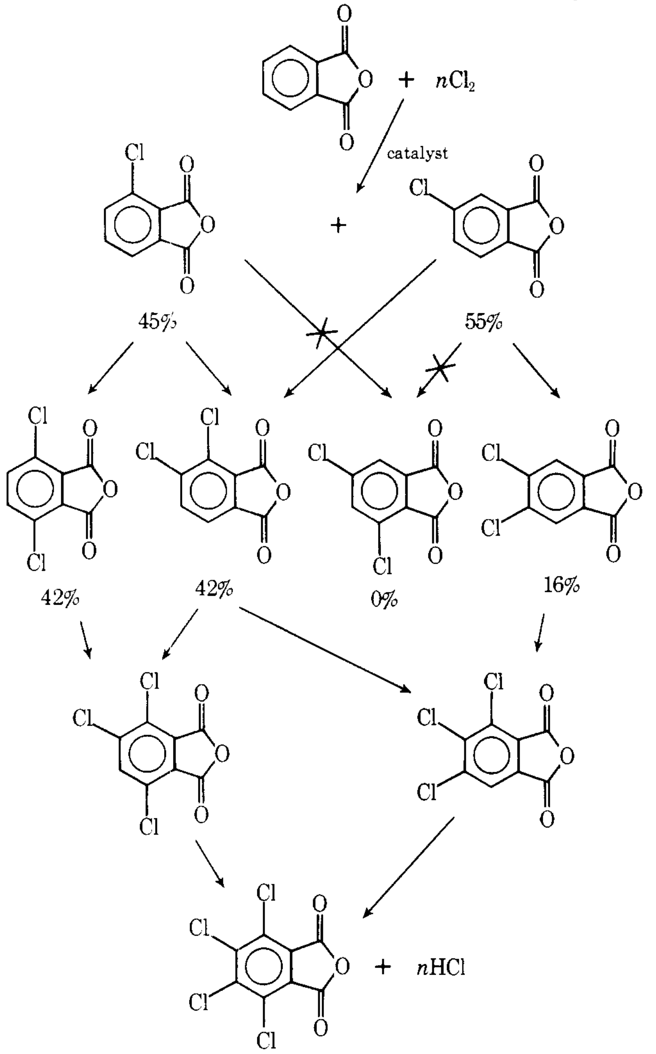
Scheme I. Products of Chlorination of Phthalic Anhydride



GLC column used (cf. Experimental section), 4,5-diClPAA proved to have precisely the same retention time as 3-ClPAA. This is consistent with the literature reports of the normal boiling points of these two compounds being identical (313 °C). With a polar GLC column (cf. Experimental Section), quantitative separation of 3-ClPAA and 4,5-diClPAA was readily achieved. No evidence for the presence of the fourth dichloro PAA isomer, 3,5-diClPAA, could be found in any of the chlorinated mixtures examined on either the polar or nonpolar GLC columns. This result is consistent with the ortho,para-directing influence of chlorine in both monochloro PAA's controlling the dichloro PAA isomer distribution. This also occurs despite the aforementioned lack of influence of the chlorine substituents on the rate of reaction. As illustrated by Scheme I, both monochloro PAA's can only yield 3,5-diClPAA through substitution meta to the chlorine already on the ring.

The data obtained from analysis of a typical PAA chlorination as it proceeded is reported in Table I, and a plot of weight percentages of the reaction mixture components as a function of the time period of chlorination is shown in Table I. The ratio of 4,5/3,4/3,6-diClPAA's remained consistently in the region of 16:42:42 before appreciable amounts of trichloro PAA's formed. An accurate quantitation of the relative rates of reactions of the dichloro PAA's was prevented by overlap of the GLC peak of 3,6-diClPAA with that of a product with a longer retention time, assigned to 3,4,5-triClPAA. The overall picture for the latter stages of the chlorination is also consistent. The presence of only two more GLC peaks with even longer retention times, the first assigned to 3,4,6-triClPAA and the last, confirmed by comparison with an authentic sample, assigned to tetrachloro PAA,[9] indicates that no significant amount of side reactions occurred.

To evaluate the possibility of isomerization among the chlorophthalic anhydrides as a possible side reaction during chlorination, experiments were conducted in which samples of 3-ClPPA, and 4-ClPAA, and chlorinated PAA mixtures were heated to 200–220 °C for periods up to 6 h in the presence of anhydrous $FeCl_3$ in the absence of chlorine. GLC analysis indicated no isomerization of any of the chloro PAA's present. Chlorinated PAA mixtures were also heated in the presence of 50 wt % of 5% palladium on carbon at 235 °C for 5 h with no change in the weight percent distribution of the original mixtures.

In an effort to alter the ratio of products, several attempts were also made to achieve free-radical chlorination of PAA through UV irradiation, but the reaction could not be induced under these conditions, even at 235 °C.

Isomer Separation. Although 4,5-diClPAA is produced to the extent of only 16% of the dichloro PAA's isomers and is thus only a minor (3–4%) component of the average monochlorinated PAA as in sample B of Table I, it represents, under such circumstance, almost 10% of the weight of 3-ClPAA. While the latter can be separated from the other components of the chlorinated mixture by fractional distillation, the presence of a 10% level of impurity makes it of unacceptable quality for most purposes. Exploratory efforts to achieve a facile nondistillative separation of 3-ClPAA from the other components of the crude monochlorinated mixture or from 4,5-diClPAA proved unsuccessful. Fractional recrystallization from *tert*-amyl alcohol, fractional melting, extraction, and sublimation were all tried without success. An alternative procedure is to chlorinate PAA to a less than average monochlorination level and thereby minimize dichlorination. This possibility was examined more closely in another chlorination

Table I. Chlorination of Phthalic Anhydride[a]

	weight %						
sample	A	B	C	D	E	F	G
reaction time, h	4	7	10	10.75	12.50	16.25	17.75
phthalic anhydride (PAA)	83.2	25.0	4.7	1.6	0.6		
4-chloro PAA	9.8	32.2	31.7	27.0	19.5	4.5	2.3
3-chloro PAA	7.0	24.9	19.0	17.6	14.0	12.3	12.8
4,5-dichloro PAA		2.5	6.0	7.0	8.2	8.5	8.5
3,4-dichloro PAA		7.7	18.4	21.9	25.1	25.9	25.6
3,6-dichloro PAA		7.7	18.4	21.9	25.2	30.4	29.9
3,4,5-trichloro PAA			–				
3,4,6-trichloro PAA				3.0	7.3	14.8	16.3
tetrachloro PAA						3.6	4.6

[a] Reaction conditions: reactant, 148 g of phthalic anhydride (1.00 mol); catalyst, 2.0 g of anhydrous $FeCl_3$ (0.012 mol); solvent, 5 mL of tetrachlorethane; and temperature, 235–240 °C.

Table II. Chlorination of Phthalic Anhydride[a]

	weight %								
sample	A	B	C	D	E	F	G	H	I
reaction time, h	4	5.75	10.25	15.25	18.25	20.25	22.25	25.5	28.5
phthalic anhydride (PAA)	81.6	80.1	63.7	44.0	40.6	34.9	30.8	27.2	24.2
4-chloro PAA	10.4	11.1	18.6	25.1	28.3	30.8	31.3	32.0	32.5
3-chloro PAA	8.0	8.8	15.9	21.2	21.9	21.6	23.2	22.7	23.0
4,5-dichloro PAA			0.2	1.1	1.3	1.8	2.0	2.5	2.9
3,4-dichloro PAA			0.8	3.3	4.0	5.5	6.4	7.8	8.7
3,6-dichloro PAA			0.8	3.3	4.0	5.5	6.4	7.8	8.7

[a] Reaction conditions: reactant, 1036 g of phthalic anhydride (7.00 mol); catalyst, 14 g of anhydrous $FeCl_3$ (0.086 mol); solvent, tetrachloroethane (5–10 mL); and temperature, 225–230 °C.

study, the data for which is shown in Table II. As can be seen from samples C and D of Table II, lower conversion of PAA can reduce the fraction of 4,5-diClPAA expressed as a percentage of 3-ClPAA to 5% or less. Fractional distillation can then be used to separate reasonable quality 3-ClPAA. Such a procedure requires recirculation of PAA and separation of 4-ClPAA, but it may still be more convenient than the nitration route for making 3-ClPAA in quantity.

Experimental Section

Chlorination of Phthalic Anhydride (Typical Procedure). A 2-L three-neck flask connected to a gas inlet, stirrer, and condenser–gas outlet was charged with 1036 g (7.0 mol) of commercial grade phthalic anhydride. The flask was heated in an oil bath to 200 °C, at which time 14 g (0.08 mol) of anhydrous ferric chloride and 10 mL of 1,1,2,2-tetrachloroethane were added. Refluxing tetrachloroethane returned sublimed PAA to the reaction vessel during the course of the chlorination. Chlorine from a cylinder was bubbled through the reaction mixture which was heated to and maintained at 225–230 °C. Small aliquots were removed at periodic intervals, dissolved in acetone, and analyzed by GLC.

3-Chlorophthalic Anhydride. A commercial sample of 3-chlorophthalic anhydride (mp 121–123 °C) was recrystallized from *tert*-amyl alcohol, mp 125–126 °C (reported mp 122 °C). Characteristic infrared peaks (Nujol mull) were seen at 1145, 1155, and 1360 cm^{-1}.

4-Chlorophthalic Anhydride. A 100-mL three-neck microflask fitted with a stirrer, gas inlet, and condenser was charged with 15 g of commercial (Aldrich) 4-nitrophthalic acid (0.071 mol). The solid was melted and heated for 2 h at 180 °C to allow conversion to the 4-nitrophthalic anhydride, and then it was heated to 240 °C while chlorine gas was bubbled through the melt. Aliquots were removed at periodic intervals for analysis by GLC, and the reaction was terminated after 6 h when samples showed identical spectra. The reaction mixture (consisting of about 80% of 4-chloro and 20% of 3-chloro PAA) was recrystallized twice from *tert*-amyl alcohol to yield 3.0 g of 4-chlorophthalic anhydride (mp 94–96 °C; reported mp 98 °C), which analyzed as >99% pure by GLC. Characteristic infrared peaks (Nujol mull) were seen at 1250 and 1335 cm^{-1}.

3,6-Dichlorophthalic Anhydride. A late distillation fraction of a chlorinated PAA reaction mixture consisting predominantly of dichlorophthalic anhydrides was recrystallized from *tert*-amyl alcohol (10 g/200 mL) to collect 2.3 g of 3,6-dichlorophthalic anhydride (mp 184–187 °C; reported mp 190–191 °C), which analyzed as 97.9% pure by GLC. Characteristic infrared peaks (Nujol mull) were seen at 615, 845, 1150, and 1220 cm^{-1}. The NMR spectrum showed a single peak at δ 8.00 in deuteriochloroform.

4,5-Dichlorophthalic Anhydride. A sample was prepared following a literature procedure. A chlorinated reaction mixture (10 g) containing 35.6% of 4,5-diClPAA (obtained by chlorinating 4-chloro PAA for 5.5 h) was heated in 50 mL of 97.3% concentrated H_2SO_4 for 1.5 h at 100–110 °C. The resulting mixture upon cooling was poured into 100 g of ice with stirring to precipitate a white solid which was washed with water and dried. The solid was triturated overnight with toluene. The toluene-insoluble fraction was recrystallized from water to yield 1.7 g of 96% pure (GLC) 4,5-dichlorophthalic acid (mp 190–193 °C).

The acid was heated to 210 °C for 3–4 h and cooled, and the product recrystallized from carbon tetrachloride to yield 4,5-dichlorophthalic anhydride, mp 182–185 °C (reported mp 185–187 °C).[10] Characteristic infrared peaks (Nujol mull) were seen at 612, 718, 1315, and 1385 cm^{-1}.

3,4-Dichlorophthalic Anhydride. This known compound[10] was identified in late distillation fractions through its characteristic NMR spectrum. In hexadeuterioacetone, 3,4-diClPAA exhibited a characteristic AB quartet with proper intensities: δ 8.20 (H_6), 8.03 (H_5) (J = 8 Hz). The intensity of the quartet in the NMR spectrum relative to the intensity of the protons of 3,6-diClPAA at δ 8.00 in the same distillation fractions was proportional to the GLC areas at 7.1 and 7.5 min, respectively, under the conditions described below.

GLC Conditions. Most analyses were performed on a 10 ft × 1/8 in stainless steel 20% QF-1 on 90–100 mesh Anchrom ABS column. The column temperature was programmed for 4 min at 195 °C, increasing to 250 °C at 20 °C/min. With a carrier (He) gas flow rate of approximately 20 mL/min, the approximate retention times of reaction mixture components are as follows: PAA, 4.0 min; 4-ClPAA, 5.0 min; 3-ClPAA, 6.2 min; 4,5-diClPAA, 6.2 min; 3,4-diClPAA, 7.1 min; 3,6-diClPAA, 7.5 min; 3,4,5-triClPAA, 7.6 min; 3,4,6-triClPAA, 7.9 min; and tetrachloro PAA, 8.9 min.

A 4 ft × 0.25 in stainless steel column packed with 80–100 mesh Chromosorb 101 operated at 275 °C was used for the separation of 3-ClPAA and 4,5-diClPAA by GLC. With a carrier gas (He) flow rate of >30 mL/min, the approximate retention times were found to be as follows: PAA, 13.0 min; 4-ClPAA, 19.0 min; 3-ClPAA, 26.0 min; 4,5-diClPAA, 32.0 min; 3,4-diClPAA, 43.2 min; and 3,6-diClPAA, 49.0 min.

This column appeared to deteriorate with time of operation at 275 °C, so that after ~24 h baseline drift made it unusable. Response factors were determined on both columns using weighed quantities of pure materials.

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Registry No.—PAA, 85-44-9; 4-ClPAA, 118-45-6; 3-ClPAA, 117-21-5; 4,5-diClPAA, 942-06-3; 3,4-diClPAA, 56962-07-3; 3,6-diClPAA, 4466-59-5; 3,4,5-triClPAA, 67238-14-6; 3,4,6-triClPAA, 59317-90-7; tetrachloro PAA, 117-08-8; 4-nitrophthalic acid, 610-27-5; 4-nitrophthalic anhydride, 5466-84-2; 4,5-dichlorophthalic acid, 56962-08-4.

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