Studies in Cyclophosphazenes. Part 5.[1] Influence of the Steric Requirements of the Amines on the Rate of Amination of 2,2,4,4,6,6-Hexachlorocyclotri(λ^5-phosphazene)

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The rates of reactions between the title compound and various straight-chain and branched primary and secondary amines to form the corresponding monoaminopentachlorocyclotriphosphazenes have been measured in tetrahydrofuran at different temperatures. The straight-chain primary amines all react at the same rate, but α-branched primary amines and secondary amines react more slowly. Although the entropy of activation makes the greatest contribution to the free energy of activation in all these reactions, the reduction of the rates is related to increases in the enthalpy of activation. Detailed analysis of the data supports a two-step mechanism. Comparison with data in the literature clarifies the steric course of the reaction and elucidates the role played by steric factors.

STERIC retardation has frequently been observed in preparative studies of the reactions of halogenocyclophosphazenes with amines and it has been manifested in three ways: (*i*) with bulky amines lower degrees of substitution were attained than with sterically less demanding amines;[2,3] (*ii*) to achieve the same degree of substitution more forcing conditions were needed with larger amines than with smaller ones;[2,3] and (*iii*) the stereochemistry of the reactions, *i.e.* the distribution of *gem*, *cis*, and *trans* isomers, was found to depend on steric factors.[3,4] These three effects can result either from the steric influence of the amine substituent already on the ring, or from that of the substituting amine, or from both of these together. Synthetic aspects of this distinction between the functions that amines can fulfil have been discussed in a recent review.[3]

Quantitative studies of steric effects in these reactions, as measured kinetically, have received less attention. Capon *et al.*[5] found that, in toluene, diethylamine reacted with hexachlorocyclotriphosphazene † more slowly than did piperidine: the reduced rate was attributed to steric factors. We showed that the differences in the rates of reaction of methylamine and of dimethylamine with hexachlorocyclotriphosphazene, with methylamino- and with dimethylamino-pentachlorocyclotriphosphazene, that arise from the operation of steric effects are associated with changes in the enthalpy of activation.[1,6] It was concluded[1] that rates of amination reactions are apparently strongly dependent on the nucleophile but virtually independent of the nature of the amine substituent in the ring, although clearly the restricted range of amines studied kinetically did not allow firm generalizations to be made.

The literature contains reports of a number of systematic studies of the influence of alkyl groups of amines on other types of reactions. Brown[7] has summarized his fundamental contributions that are, in large part, based on studies of equilibria between amines and boranes. Steric effects in nucleophilic aromatic substitution were investigated by Brady and Cropper,[8] and in replacement reactions at saturated carbon centres by Henderson and Schultz[9] and by Okamoto and his co-workers.[10,11] Dostrovsky and Halmann[12] and Keay[13] have studied the reactivities of amines in displacements at phosphorus centres.

Since the variety of amines reacting with phosphazenes has been so limited in these kinetic studies, and since the distinction between amines acting as substituents and as nucleophiles has not been examined systematically, we undertook to make up this deficiency by investigating the reactivities of a number of amines acting in both capacities. This paper is concerned with the study of amines filling the role of nucleophiles. We have been able (*i*) to find additional support for a two-step mechanism, (*ii*) to draw a picture of the steric course of these reactions including the geometries of the transition states, and (*iii*) to elucidate details of how steric effects retard the rates of these reactions. A preliminary report has appeared.[14]

EXPERIMENTAL

The preparation and purification of hexachlorocyclotriphosphazene and tetrahydrofuran (thf) have been described previously.[15] A thf solution of ethylamine was prepared from a 25—30% aqueous solution supplied by B.D.H., as reported for dimethylamine.[15] n-Butylamine, isopropylamine, diethylamine, and di-n-butylamine were B.D.H. reagent-grade products; t-butylamine and piperidine were Fluka *puriss.* reagents. All these amines were purified by heating them under reflux over K[OH] for several hours followed by distillation.

Previously described methods[6,15] were employed to prepare and standardize the solutions, to perform the kinetic runs, and to remove and quench samples. However, a different analytical method was used to determine the extent of reaction. In these experiments the amount of excess of acid in the quenching solution was determined by titrating with standardized Na[OH] an aliquot taken from the separated aqueous phase of the quenching mixture. The use of a Radiometer model TTTlc titrimeter coupled with a SBR2c Titrigraph to determine end-points overcame the problems connected with the choice and use of an appropriate indicator in the solvent mixture and assured high precision.

In the more rapid reactions that required < *ca.* 12 min for

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† A more systematic name for this compound is 2,2,4,4,6,6-hexachlorocyclotri(λ^5-phosphazene), the prefix λ^5 indicating that each phosphorus atom possesses a connecting number of five.

ca. 80% completion there was insufficient time available to remove and quench 8—10 samples, so those experiments were run in exactly the same way repeatedly, two or three samples being withdrawn and analysed in each run. The data were treated as if they had all been collected from one experiment.

RESULTS AND DISCUSSION

Table 1 presents details of the experiments performed and the calculated rate constants. The reactions were all shown to obey a second-order rate law being first order in the concentrations of both the amine and phosphazene. Average rate constants at various temperatures, the activation parameters calculated therefrom, together with other derived data, and relevant values reported in earlier studies are collected in Table 2.

The rate law and the relative magnitudes of the activation parameters, with the $\Delta S^‡$ contribution dominating, suggest that all these reactions proceed by the same mechanism that was proposed previously.[15] According to this an adduct is first formed between the phosphazene and the amine in a rapid pre-equilibrium. In the following rate-determining step this adduct decomposes with elimination of hydrogen chloride. It was proposed that the first step of the reaction accounts largely for the $\Delta H^‡$ whilst $\Delta S^‡$ is connected, primarily, with the elimination. Apparently, the same mechanism operates with all the amines in their reactions with hexachlorocyclotriphosphazene regardless of whether

TABLE 1

Details of the kinetic runs for the reactions $N_3P_3Cl_6 + 2NR(R')H \longrightarrow N_3P_3Cl_5(NRR') + [NR(R')H_2]Cl$

Expt.	Amine	$10^4[N_3P_3Cl_6]_0$	$10^4[\text{amine}]_0$	θ_c/°C	k_2 */dm^3 mol^{-1} s^{-1}
		mol dm^{-3}			
1	$NEtH_2$	0.98	1.96	30	22.9 ± 0.3
2		1.96	1.96		23.1 ± 0.4
3		0.985	1.38		23.0 ± 0.2
4	NBu^nH_2	1.115	2.23	30	23.2 ± 0.4
5		1.73	1.73		23.0 ± 0.2
6		0.695	1.39		23.0 ± 0.1
7	NPr^iH_2	4.72	4.72	30	1.31 ± 0.02
8		4.72	9.44		1.32 ± 0.02
9		4.56	6.06		1.32 ± 0.02
10	NBu^tH_2	51.3	51.3	18	0.0097 ± 0.00009
11		56.7	113.4		0.0098 ± 0.00011
12		113.4	113.4		0.00979 ± 0.00010
13		11.32	11.32	30	0.0165 ± 0.0003
14		7.50	15.0		0.0163 ± 0.0022
15		20.0	10.0		0.0161 ± 0.0003
16	NEt_2H	5.70	11.4	30	0.0663 ± 0.0002
17		9.32	9.32		0.0671 ± 0.0014
18		9.98	19.96		0.0667 ± 0.0015
19	$NBu^n{}_2H$	6.15	12.30	30	0.0593 ± 0.0018
20		19.76	19.76		0.0611 ± 0.0015
21		22.40	11.20		0.0578 ± 0.0022
22	$C_5H_{10}NH$	4.82	4.82	0	3.91 ± 0.07
23		2.41	4.82		3.96 ± 0.12
24		4.82	9.64		3.92 ± 0.08
25		4.82	4.82	18	5.89 ± 0.11
26		2.41	4.82		5.86 ± 0.08
27		0.92	0.92	30	7.40 ± 0.22
28		0.92	1.84		7.50 ± 0.27
29		0.80	1.23		7.32 ± 0.18

* For average values at each temperature see Table 2.

TABLE 2

Summary of average rate constants and activation parameters for reactions in Table 1

	k_2/dm^3 mol^{-1} s^{-1}				$\Delta H^‡$	$\Delta S^‡$	
Amine	30	20	18	10 °C	kJ mol^{-1}	J K^{-1} mol^{-1}	$-10^2(T\Delta S^‡/\Delta G^‡)$
$NMeH_2$ [a]	23.17 ± 0.58	21.17 ± 0.37		19.83 ± 0.27	2.9 ± 1.7	−205 ± 6	96 ± 2
$NEtH_2$	23.0 ± 0.3						
NBu^nH_2	23.1 ± 0.1						
NPr^iH_2	1.32 ± 0.02						
NBu^tH_2	0.0163 ± 0.0003		0.0097 ± 0.0001		28.8 ± 1.7	−184 ± 6	66 ± 2
NMe_2H [b]	11.53 ± 0.18	9.93 ± 0.23		8.78 ± 0.13	7.1 ± 2.1	−197 ± 8	88 ± 4
NEt_2H	0.0667 ± 0.0017						
$NBu^n{}_2H$	0.0594 ± 0.0018						
$C_5H_{10}NH$	7.41 ± 0.19		5.88 ± 0.09	3.93 ± 0.09 [c]	12.1 ± 2.1	−188 ± 6	83 ± 3

[a] Ref. 6. [b] Ref. 15. [c] At 0 °C.

they react by geminal or non-geminal pathways in their reactions with aminochlorocyclophosphazenes. We observed no intrinsic differences between these various types of amines.

Examination of the changes in the rates of reaction of the various types of amines at 30 °C (Table 2) shows an overall trend to lower rates of reaction with increased steric requirements. Additionally, three specific trends can be discerned. (*a*) Considering the same alkyl groups, secondary amines react more slowly than primary ones. (*b*) Chain branching at the α-carbon atom has a retarding effect that is larger than the one previously mentioned, despite the fact that the branching is one atom further removed from the reaction centre. (*c*) In contrast to findings in other reactions, lengthening of the alkyl chains in straight-chain primary amines does not appreciably affect the rates of the reactions. With the corresponding secondary amines there is a significant effect in passing from dimethylamine to diethylamine, but beyond that chain lengthening only causes slight retardation.

TABLE 3

Comparison of steric effects of amines: relative reactivities [a] in various reactions are specified

	Relative reactivity in reaction						
Amine	(1) [b]	(2)	(3)	(4)	(5)	(6)	(7)
$NMeH_2$	35 (270)		0.26	17 (831)			347 (1 423)
$NEtH_2$	17 (134)		0.20	4.8 (242)			344 (1 411)
NBu^nH_2	26 (201)	26	0.19	5.3 (263)	27 (150) [c]		346 (1 417)
NPr^iH_2	3.3 (26)			0.53 (26)			20 (81)
NBu^sH_2	3.3 (25)			0.48 (24)	11 (60)	0.30 (1.2) [d]	
NBu^tH_2	0.13 (1)			0.02 (1)	0.18 (1)	0.24 (1)	0.24 (1)
NMe_2H	57 (442)		1.75	187 (9 342)			173 (707)
NEt_2H	1 (7.8)	1	1	1 (50)	1 (5.5)	1 (4.1)	1 (4.1)
NBu^n_2H		0.75	0.54	0.94 (47)	1 (5.5)	0.7 (2.9)	0.89 (3.7)
$C_5H_{10}NH$				80.5 (4 026)			59 (241)

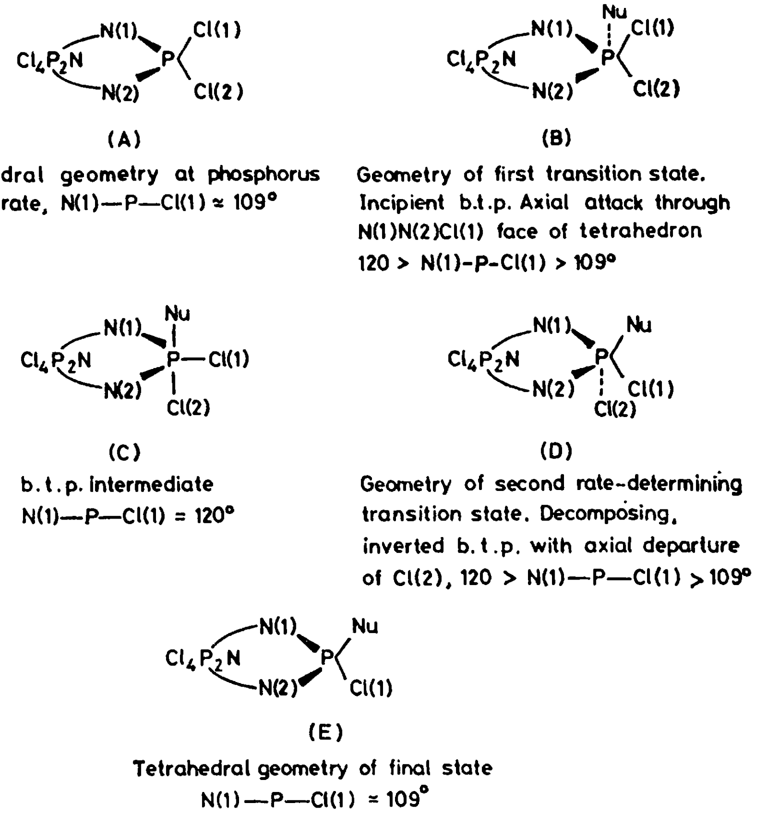
Reactions: (1) $NR(R')H + BMe_3 \xrightleftharpoons{100\ °C} NR(R')H{\cdot}BMe_3$, K(100 °C), data from ref. 7; (2) $NR(R')H + EtI \xrightarrow{Me_2CO} [NEt(R)R'(H)]I$, k_2 (35 °C), data from ref. 9; (3) $NR(R')H + MeI \xrightarrow{C_6H_6} [NMe(R)R'(H)]I$, k_2 (30 °C), data from ref. 11*a*; (4) $NR(R')H + (O_2N)_2C_6H_3Cl \xrightarrow{EtOH} (O_2N)_2C_6H_3NRR' + base{\cdot}HCl$, k_2 (25 °C), data from ref. 8; (5) $NR(R')H + PCl(O)(OPr^i)_2 \xrightarrow{C_6H_6} P(NRR')O(OPr^i)_2 + base{\cdot}HCl$, k_2 (40 °C), data from ref. 12; (6) $NR(R')H + PMe(Cl)O(OEt) \xrightarrow{Me_2CO} PMe(NRR')O(OEt) + base{\cdot}HCl$, k_2 (−25 °C), data from ref. 13; (7) $NR(R')H + N_3P_3Cl_6 \xrightarrow{thf} N_3P_3Cl_5(NRR') + base{\cdot}HCl$, k_2 (30 °C), this work.

[a] Values normalized to diethylamine, the only amine common to all reactions. Values in parentheses are relative to t-butylamine, the most sterically hindered amine. [b] Relative equilibrium constants (not rate constants). [c] At 25 °C. [d] At −48 °C.

This picture can be understood by analysing it in terms of Brown's separation of steric effects into frontside (F) and backside (B) interactions.[7] Since, with primary amines, B effects can at most be minor, the substantial influence of chain branching in primary amines must be due very largely to F effects, namely those caused by repulsions between the methyl groups of the isopropyl- and t-butyl-amines and the phosphorus atom and those atoms bonded to it, *i.e.* the two adjacent ring-nitrogen atoms and the one chlorine atom on the same side of the ring attacked (assuming that attack is roughly perpendicular to the plane of the ring, see below). Additionally, repulsive interactions with the other two chlorine atoms on the same side of the ring may make a contribution. Unbranched primary amines do not, of course, cause any such interactions and were indeed found to have uniformly high reactivity. A combination of B and F effects is presumably responsible for the retardation observed with secondary amines. Taking a specific example, the similar reactivity of methyl- and ethyl-amine on the one hand, and the differences between dimethyl- and diethyl-amine on the other, are explicable in these terms. There are no conformations of diethylamine as bonded in the transition state in which B interactions between its two methyl groups and the above F effects can be totally prevented. The absence of these B repulsions in ethylamine, methylamine, and dimethylamine in their corresponding transition states enables the entire situation to be understood. The differences of reactivity between diethylamine and piperidine reported in this and an earlier study [5] and the similarity between the reactivity of the latter amine and dimethylamine support this interpretation. Study of the repulsions in all the above cases using space-filling models shows that interatomic distances which approach, and are often smaller than, the sums of the van der Waals radii do occur. In branched-chain secondary amines it can be expected that considerable F effects will be reinforced by strong B effects leading to very sluggish reactions. In fact these amines reacted too slowly for the reactions to be conveniently followed by the techniques we used. Furthermore their preparative behaviour, as reported for example for di-s-butylamine,[2] di-isobutylamine,[2] dicyclohexylamine,[2] and dibenzylamine,[16] is fully consistent with this interpretation.

It is tempting to try and compare the above trends, at least qualitatively with those found in other aminations investigated. Pertinent relative rate data are assembled in Table 3. In the other systems the first effect (primary *versus* secondary amines) is shown by certain amines, but its reverse is observed with others. No exception to the second trend (chain branching) has been reported in the reactions being compared. The third trend (chain-lengthening effects) was also found by Brown[7] and by Brady and Cropper:[8] however, on the evidence available, a detailed comparison of this third point in the other systems considered does not seem justified. No more qualitative comparisons are possible, amongst other reasons because the steric changes in reaching the transition states in the various reactions are different, as will be explained below.

A comparison of the magnitudes of the relative rates in all these reactions reveals that the relative retardation observed in this study is generally greater than in the others, except in displacements at phosphorus. This can be understood as follows. In the present aminations, displacement is thought to proceed by attack perpendicular to the plane of the ring with resulting inversion. This is effectively equivalent to attack through the ' top ' face of the tetrahedron of atoms surrounding the phosphorus atom. This mode of attack is supported by several lines of evidence.[17] It has also been found in displacement of chlorine by amines at phosphorus in other six-membered heterocycles.[18] Then assuming a two-step reaction, the Scheme illustrates the steric changes taking place from (A) to (E).



(A)

Tetrahedral geometry at phosphorus in substrate, N(1)—P—Cl(1) ≈ 109°

(B)

Geometry of first transition state. Incipient b.t.p. Axial attack through N(1)N(2)Cl(1) face of tetrahedron 120 > N(1)-P-Cl(1) > 109°

(C)

b.t.p. Intermediate N(1)—P—Cl(1) = 120°

(D)

Geometry of second rate-determining transition state. Decomposing, inverted b.t.p. with axial departure of Cl(2), 120 > N(1)—P—Cl(1) > 109°

(E)

Tetrahedral geometry of final state N(1)—P—Cl(1) = 109°

SCHEME Changes in geometry at the centre attacked during the course of the reaction. Partial changes have been omitted for simplicity. Nu = Amine, b.t.p. = bitrigonal pyramid

The first transition state (B) is the decisive one with respect to steric hindrance. In addition to it differing geometrically from those involved in reaction at carbon and boron in having a higher co-ordination number (except for saturated carbon), it is also appreciably more compressed than all the others.[17b] The structure (B) with its implied large F interactions is then consistent with the relatively strong steric hindrance found in this study and with the relative reactivities of methyl- and dimethyl-amine with phosphazenes found earlier, from which it was deduced that steric effects overweigh others.[6] Moreover, generally, (B) can only describe the first transition state in reactions at tetrahedral P^V if they proceed by a two-step associative mechanism, but it cannot apply if a one-step mechanism operates. The latter mechanism, a modified S_N2 mechanism, as proposed by Hughes[19] has been assumed in some previous investigations.[12,13] However, inspection of the relative rates in displacements at phosphorus for all amines for which comparison is possible (Table 3) shows a strikingly close similarity in the magnitudes of the relative rates and suggests a common transition state and mechanism. A re-examination of the assumption of a one-step mechanism is warranted in the light of the above and of other evidence that we summarized for a two-step mechanism.[15] The reasoning used was very similar to that so persuasively argued by Swain *et al.*[20] for a similar situation pertaining to silicon. Furthermore, recent direct evidence supports the existence of an intermediate in displacement at phosphorus in phosphinates.[17b,21]

Examination of the $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values (Table 2) shows that the steric retardation is due solely to increased values of $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$ actually increasing as $\Delta H^{\ddagger}$ increases. This latter finding favours a two-step mechanism since it is incompatible with a one-step reaction mechanism, Taft[22] having shown that steric retardation connected with a rate-determining transition state results in lower values of $\Delta S^{\ddagger}$. Indeed we have argued from the very low values of $\Delta S^{\ddagger}$ calculated that the ionization step, which is identical for all the amines, is rate determining, in conformity with Pearson's[23] conclusion that ion formation imposes stringent solvation requirements and is therefore connected with very low values of $\Delta S^{\ddagger}$. The inverse relationship between $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ can be rationalized by realizing that the greater the steric repulsions in the intermediate (C) the greater the steric acceleration in its decomposition. The additional energy of the intermediate activates fission of the bond to the departing, incipient, chloride ion. This in turn reduces the need for solvation of the transition state, leading to higher values of $\Delta S^{\ddagger}$ that are inversely proportional to the values of $\Delta H^{\ddagger}$. It must be pointed out that the steric acceleration referred to above differs intrinsically from that operating in S_N1 reactions because the departing chloride ion is totally isolated from the source of the steric interactions since the two ring-nitrogen atoms and Cl(1) screen it from any direct interaction with the alkyl groups of the amine. This steric acceleration can therefore be expected to be quite moderate compared with the retardation operative in the first transition state (B).

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