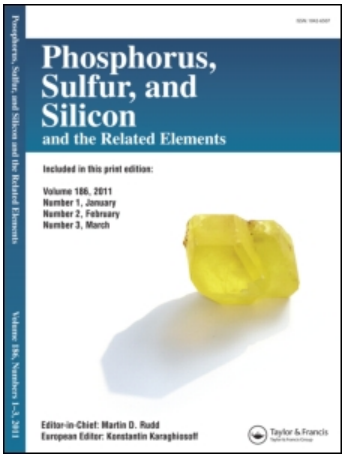

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"DRY MEDIA PROCESS": A CHEMAC (CHEMICAL MACHINERY) FOR THE AMINOLYSIS OF HEXACHLOROCYCLOTRIPHOSPHAZENE ON SOLID SUPPORTS

Fraņois Sournies[a]; Marcel Graffeuil[a]; Bénédicte Séguès[a]; Fraņois Crasnier[a]; Delphine Semenzin[b]; Guita Etemad-Moghadam[b]; Max Koenig[b]; Jean-Fraņois Labarre[a]
[a] Laboratoire Structure et Vie (LSEV), Université Paul Sabatier, Toulouse, Cedex, France [b] Laboratoire d'Activation Moléculaire par l'Electricité, le Rayonnement et l'Energie Sonore (AMPERES), Université Paul Sabatier, Toulouse, Cedex, France

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FRANÇOIS SOURNIES,† MARCEL GRAFFEUIL,†
BÉNÉDICTE SÉGUÈS,† FRANÇOIS CRASNIER,†
DELPHINE SEMENZIN,‡ GUITA ETEMAD-MOGHADAM,‡
MAX KOENIG‡ and JEAN-FRANÇOIS LABARRE†*

†Laboratoire Structure et Vie (LSEV), Université Paul Sabatier, 118 route de Narbonne, 31062 Toulouse Cedex, France; ‡Laboratoire d'Activation Moléculaire par l'Electricité, le Rayonnement et l'Energie Sonore (AMPERES), Université Paul Sabatier, 118 route de Narbonne, 31062 Toulouse Cedex, France

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Aminolysis of $N_3P_3Cl_6$ by lipophilic long-chain monoamines runs regiospecifically when achieved on some suitable solid supports constituted from impregnated or not alumina and it allows the synthesis in a very neat way of some aminocyclophosphazenes of interest as precursors of new bio-materials.

Key words: Cyclotriphosphazene; regiospecific aminolysis; dry media; alumina supported reaction; mechanism of dry media processes; molecular modeling.

INTRODUCTION

Aminolysis of hexachlorocyclotriphosphazene, $N_3P_3Cl_6$ **1** (Figure 1), by lipophilic primary amines **2** leads to twelve configurations **3** to **14** which cannot be obtained by any mean in a regiospecific way. Indeed, every configuration is currently synthesized with some others as by-products and aminolysis needs commonly 48 hours at least to be achieved when performed at room temperature. Thus, several attempts at the regiospecific production of aminocyclotriphosphazenes of biological interest as anticancer and/or immuno-modulating drugs have been made in our Group during the last decade with the aim of lessening the time-and-money consuming character of the obtention of pure such chemicals.[1]

The present contribution reports on the successes we got on suitable solid supports upon aminolysis of hexachlorocyclotriphosphazene, $N_3P_3Cl_6$, by lipophilic amines such as $C_8H_{17}NH_2$ and $C_{12}H_{25}NH_2$. These peculiar aminolyses will constitute the basic scheme for the settlement of a general chemical machinery (coded as CHEMAC) of such reactions.

*Author for correspondence; also all authors belong to the Institut de Chimie Moléculaire Paul Sabatier of CNRS.

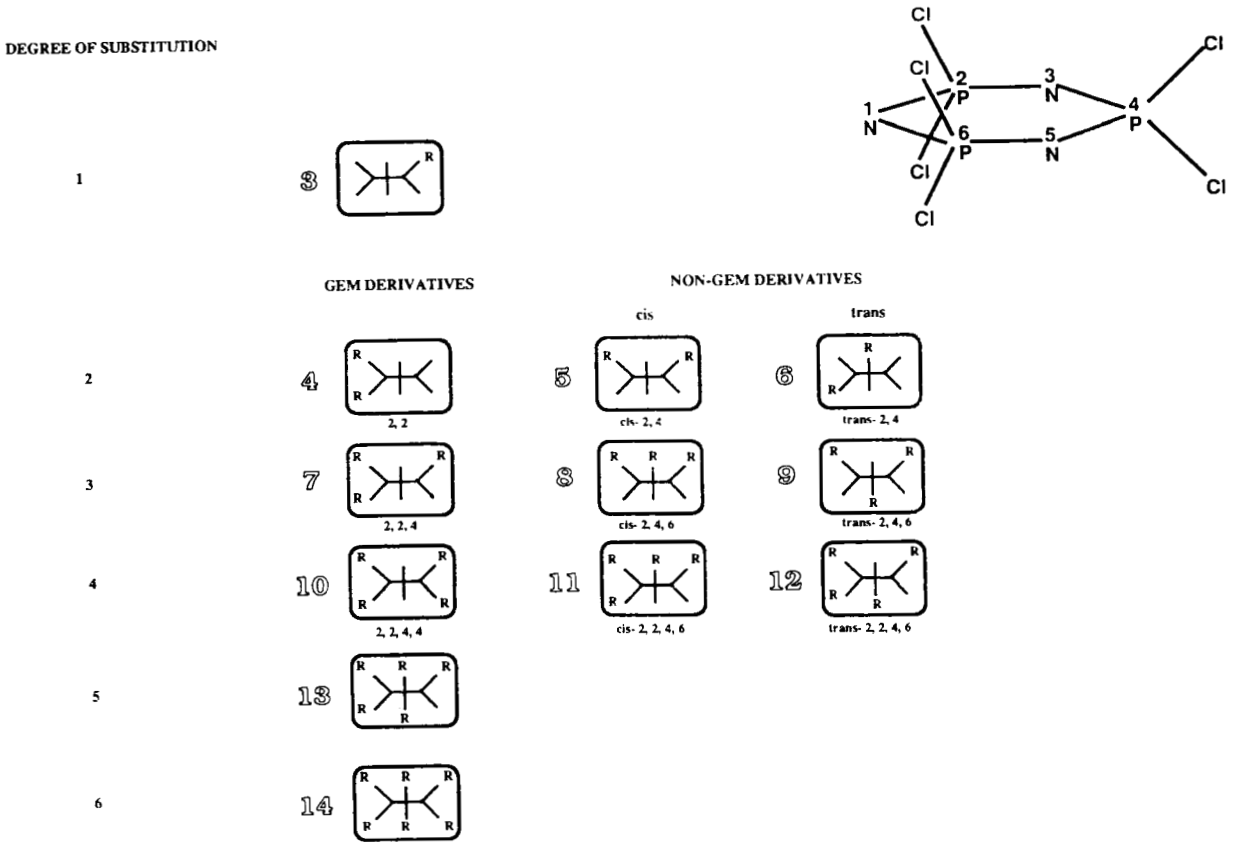

FIGURE 1 Predictable configurations from aminolysis of $N_3P_3Cl_6$.

AMINOLYSIS OF $N_3P_3Cl_6$ BY OCTYLAMINE AND/OR DODECYLAMINE IN HOMOGENEOUS CONDITIONS

The choice of octylamine $C_8H_{17}NH_2$ and/or dodecylamine $C_{12}H_{25}NH_2$ for this study is in keeping with the general pattern of vectorized anticancer drugs we are dealing with. Indeed, a way of targeting cyclophosphazenic drugs may go through their linkage to low density lipoproteins (LDL) as homing heads for malignant cells but such an approach needs the existence in cyclophosphazenic structures of two or four lipophilic chains grafted in a gem position (4- and 10-type derivatives) on the ring. Actually, the synthesis of such hindered configurations is challenging chemists according to the repulsive trend of lipophilic chains when they are close together. Molecular modeling shows indeed that such gem configurations request a complete unfolding of the two chains which is about 10 kcal. mol-1 less stable than the common staggered configurations which characterize free amines.[2]

Anyhow, let us consider aminolysis of $N_3P_3Cl_6$ by octylamine through the following homogeneous pathway:

$$\underset{\mathbf{1}}{1N_3P_3Cl_6} + \underset{\mathbf{2}}{2C_8H_{17}NH_2} \rightarrow \underset{\mathbf{4,\ 5,\ or\ 6?}}{N_3P_3Cl_4(C_8H_{17}NH)_2} + 2HCl.$$

Such a reaction, commonly achieved in toluene as the solvent with Et_3N for picking up hydrogen chloride, was stopped when the ^{31}P NMR spectrum of the crude product remained unchanged in time, that is two days later. The clear organic phase was then poured off and the solvent was removed in vacuo at 25°C to give a yellow syrup containing a medley of (i) **4** (30%), (ii) **10** (30%), and (iii) other substituted products (40%). The whole components of the final crude product were evidenced by ^{31}P NMR according to the standard data of literature on cyclophosphazenes.[3]

Thus, aminolysis of $N_3P_3Cl_6$ **1** by octylamine **2** is neither regiospecific nor even regioselective and the final mixture is so intricate that no attempts at the partition of its components might be reasonably envisaged.

What happens now when the same reaction is achieved still in toluene but now with a convenient solid support for picking up HCl?

Actually, it is well-known indeed that a wide variety of chemical reactions can be promoted in heterogeneous media thanks to the acidic and/or basic sites located on the surface of suitable solids such as alumina, clay, silica gel, talc and others.[4] The significant advantages of such "solid support" reactions relatively to the corresponding homogeneous reactions are the milder conditions, the more specific (chemospecific, regiospecific and stereospecific) transformations and the easier isolation of final pure products.

AMINOLYSIS OF $N_3P_3Cl_6$ BY OCTYLAMINE AND/OR DODECYLAMINE ON BASIC ALUMINA

The basic alumina we used (coded as BASAL) was provided by FLUKA (Reference 06290 type 5016 A basic, pH 9.5 ± 0.2).

As a typical experiment, such a basic alumina (without any peculiar treatment)

was impregnated with a toluene solution of the two starting materials, $N_3P_3Cl_6$ **1** and octylamine **2**, in the (1:2) ratio. The solvent was immediately removed in vacuo at 25°C, throwing so reagents down to the alumina surface. A simple washing of the solid support with toluene as the eluent yields the final product which is the mono-substituted $N_3P_3Cl_5R$ compound **3** (70%) contaminated with the non-reactive $N_3P_3Cl_6$ **1** which was easily recovered if hexane is firstly used as eluent ($N_3P_3Cl_6$ being highly soluble in it when **3** is not) followed by toluene extraction for the specific elution of **3**. In other words, it may be concluded that basic alumina as the solid support makes aminolysis of **1** by **2** regiospecific, the final product being the mono-substituted derivative **3** and not its disubstituted relatives **4** to **6**. This means probably that one of the two molecules of octylamine was used for picking up HCl from the reaction, the role of alumina being essentially to force aminolysis in a regiospecific way. This assumption is supported by the fact that when reaction occurs in (1:4) stoichiometric conditions, the mono-substituted moiety **3** is still obtained as the major product (80%) with several non-gem by-configurations as impurities (20%).

Whatever the improvements demonstrated so by using basic alumina as the solid support, the expected gem disubstituted $N_3P_3Cl_4R_2$ **4** entities we need for linkage to LDL could not be obtained here. Then, we got the idea that suitable impregnations of basic alumina by a real strong base such as potassium hydroxide would both keep the regiospecific impulse of alumina and set the second molecule of octylamine free for further (gem?) substitution.

This is actually the case, as demonstrated in the next section.

AMINOLYSIS OF $N_3P_3Cl_6$ BY OCTYLAMINE AND/OR DODECYLAMINE ON ALUMINA-SUPPORTED POTASSIUM HYDROXIDE

According to the same workup than above described, the reaction in the (1:2) ratio was achieved on alumina-supported potassium hydroxide instead of the basic alumina. The constitution of the crude final product obtained after elution of the mixture was determined by ^{31}P NMR. The gem $N_3P_3Cl_4R_2$ **4** and the gem-gem $N_3P_3Cl_2R_4$ **10** configurations were obtained as the main products. Moreover, the **4/10** ratio was evidenced as depending drastically (i) on the dried degree of the solid support and (ii) on the amount of potassium hydroxide impregnated on alumina: for example, the ^{31}P NMR spectrum of the crude final product we obtained when using a dry (i.e. dried for 24 h in oven at 70°C) alumina (FLUKA, Reference 06300, pH 7.0 ± 0.5)/KOH (50g:11g) solid support [coded as ALPOT (50:11)] reveals the **4** and **10** configurations in the (90%:10%) ratio, **4** appearing as the major product. Incidentally, it was possible to get the latter by a mere SiO_2 column chromatography only if the crude final mixture was octylamine-free. Indeed, we observed that if the column chromatography was achieved in presence of free octylamine in the medium, a secondary reaction on SiO_2 as the solid support happened which transformed **4** into **10**.

What happens now when the amount of KOH impregnated on alumina increases? Several features may happen but the neatest pattern is observed when using an ALPOT (50:50) as the dry medium: indeed, **10** is obtained in a stereospecific way

and this result is definitely amazing when thinking that this peculiar configuration belongs actually to a set of ten possible (from mono to tetra) configurations as demonstrated in Figure 1.

Coming back to the genuine purpose of this work, that is to the attempt at the production of the gem disubstituted **4** and gem-gem tetrasubstituted **10** octylaminocyclophophazenes in a regiospecific manner, the present state of our works shows that we were able to discriminate the optimal ratio of KOH impregnated on alumina leading to the second moiety in a pure state and the former one also but in a selective way only. This assertion is basically correct when aminolysis is performed in (1:2) stoichiometric conditions. Actually, we could make the synthesis of **4** regiospecific by decreasing the amount of octylamine involved in the reaction: (1:1.6) ratio leads indeed to pure **4**. In other words, aminolyses on such supports are so quick and drastic that a lack of amine has to be used with respect to the stoichiometry which would be needed for a given synthesis, the excess of $N_3P_3Cl_6$ being never observed on ^{31}P NMR patterns.

Thus, aminolysis of $N_3P_3Cl_6$ by octylamine on basic alumina and on alumina-supported potassium hydroxide yields stereospecifically to some given configurations only among the wide set of predictable ones. This constitutes an unquestionable improvement *versus* what happens in homogeneous synthetic conditions but the role of alumina as the support stayed disputable as long as we had not investigated aminolysis in presence of potassium hydroxide alone. Then, aminolysis was performed in this way and leads to the monosubstituted derivative **3** in a regiospecific way, that is exactly to the same result as the one we obtained previously with basic alumina itself. Consequently, alumina-supported KOH constitutes a real supramolecular solid support which has definitely nothing to do with basic alumina on one side and potassium hydroxide on the other.

Whatever these successes in designing suitable experimental conditions for the production of the expected gem-aminocyclophosphazenes **4**, we have to admit that these conditions were discriminated according to a sort of "success story." Indeed, the number of parameters (nature of the solid support, nature of the base, rate of base impregnation, stoichiometry of reactants, solvent for starting materials deposit on the solid support, solvent for elution, degree of moisture and so on) is so large that a researcher, even graduate, could spend years and years dealing hard with this subject without getting any decisive result.

In other words, we had to gather the whole experiments we did in our Group during the last year in the hope of settling a general mechanism capable of accounting for the whole results and of allowing safe predictions for further works.

On a first step, we shall detail several queries we were urged to ask ourselves with reference to our results. On a second step, we shall shuffle replies to these queries and we shall propose in this way the expected CHEMAC.

QUERIES AND REPLIES

We mentioned above that aminolysis of $N_3P_3Cl_6$ by octylamine and/or dodecylamine in the (1:1.6) stoichiometry on ALPOT (50:11) as the solid support yields instantaneously the pure gem-disubstituted entities **4** when toluene is used as the eluent.

Remember too that the ^{31}P NMR singlet at 20.1 ppm, corresponding to the excess of $N_3P_3Cl_6$ [with respect to the (1:2) stoichiometry], is never observed even when increasing the excess of $N_3P_3Cl_6$ as it is the case for stoichiometries such as (1:1.5), (1:1) or even (1:0.8). The use of (1:0.5) conditions has to be made to reveal the $N_3P_3Cl_6$ singlet.

Thus, a first query arises: is $N_3P_3Cl_6$ not observed on the NMR pattern because (i) either its unreactive part remains adsorbed on the solid support (ii) or it has generated some other amino side-products which are adsorbed by themselves on the ALPOT (iii) or it has wholly generated only the gem-disubstituted entities **4** a certain amount of which remains adsorbed on the ALPOT? A very simple reply may be done in this way: (i) pure $N_3P_3Cl_6$, previously deposited alone on ALPOT from a toluene solution, is partly recovered upon a common elution in sequence with toluene and (ii) both gem and non-gem products (previously isolated in a pure state from other experiments) are partly recovered too upon elution with toluene. It must be pointed out that the average rate of recovery was about 75% in every case (under the express condition that 3 successive washings at least were performed). In other words, the non-observation of the 20.1 ppm singlet we evoked above is definitely due to a total transformation in gem derivatives which are partly adsorbed on ALPOT and neither to a retention of $N_3P_3Cl_6$ itself or to a retention of non-gem entities on ALPOT.

Incidentally, the same experiment with $N_3P_3Cl_6$ (i.e. deposit followed by elution with toluene) may be repeated on non-impregnated alumina such as basic alumina or genuine alumina. The final result stays unchanged: $N_3P_3Cl_6$ may be recovered in both cases. We shall need this peculiar result for further discussion below.

Then, a second query arises: is it possible to approach the way $N_3P_3Cl_6$ is lying on the solid support upon deposition? A skillful answer may be provided here too as following: when octylamine and/or dodecylamine are deposited (through solutions in toluene) on ALPOT previously impregnated with $N_3P_3Cl_6$, the ^{31}P NMR pattern of eluted species reveals one singlet (and only one) at 18.3 ppm which corresponds to the hexasubstituted moiety **14** (as demonstrated by DCI/NH_3 mass spectrometry) whatever the (1:x) (x varying from 1.6 to 6) stoichiometry we used. That means that $N_3P_3Cl_6$ is probably sticked as shown in Figure 2 through a N →

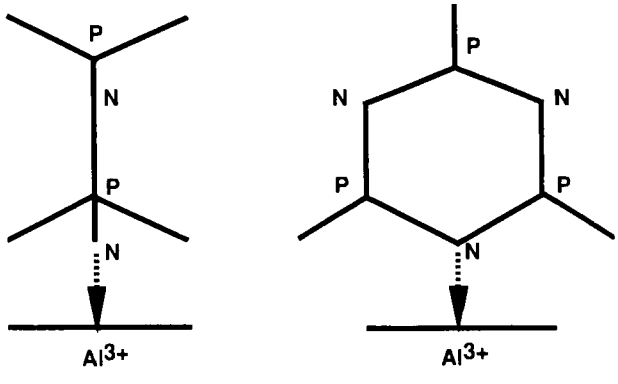

FIGURE 2 Adsorption of $N_3P_3Cl_6$ on Alumina (impregnated or not): the N → Al dative bond is weak enough to be broken upon elution by toluene.

Al dative bond analogous to the one which was clearly evidenced by X-Ray investigation of the $N_3P_3Cl_6 \cdot AlBr_3$ adduct.[5] Incidentally, such a coordinative process lessens sharply the electron density into the related PNP endocyclic Dewar island, providing so the N_3P_3 ring with a noticeable cyclophosphazanic character. In such conditions, the N_3P_3 ring loses to some extent its rigidity (planarity), allowing its phosphorous atoms to gain a larger degree of flexibility which favours their capability to pseudo-rotations (according to Gielen, Ramirez and Berry) which are needed by $S_N2(P)$ aminolyses. This prime element of the CHEMAC we shall detail below makes the obtention of the hexasubstituted moiety **14** conspicuous, approaches of amines occurring with the same probability on both sides of the N_3P_3 ring.

Anyhow, if some non-gem by-products were generated besides the gem derivatives when aminolysis occurs on ALPOT in (1:1.6) stoichiometric conditions, they stay adsorbed on the solid support through the pattern of Figure 3 which is strongly stabilized by hydrogen bondings between NHR groups and OH^- sites of ALPOT. The existence of these stabilizing interactions keeps these non-gem moieties refractory to elution. A decisive proof of the validity of this assumption may be found by repeating the experiment [both $N_3P_3Cl_6$ and amine in (1:1.6) conditions deposited together] on a non-impregnated alumina. We demonstrated above that non-gem configurations were eluted. Figure 4 explains why: no more hydrogen bondings between the cyclophosphazene and the solid support (absence of OH^- sites) and, as a consequence, an easy elution by toluene.

Finally, we have to understand how (fourth query) the gem disubstituted **4** and tetrasubstituted **10** chemicals, which are revealed from aminolysis on ALPOT, may be so easily eluted by toluene. According to Figure 3, we would have predicted that such a gem derivative **4** would be sticked on the solid support much stronger yet than its non-gem cousin because of twice more hydrogen bondings. Actually, Figure 5 provides the reply: when a second molecule of RNH_2 attacks on the phosphorus atom which was already aminolyzed, the well-known "proton abstrac-

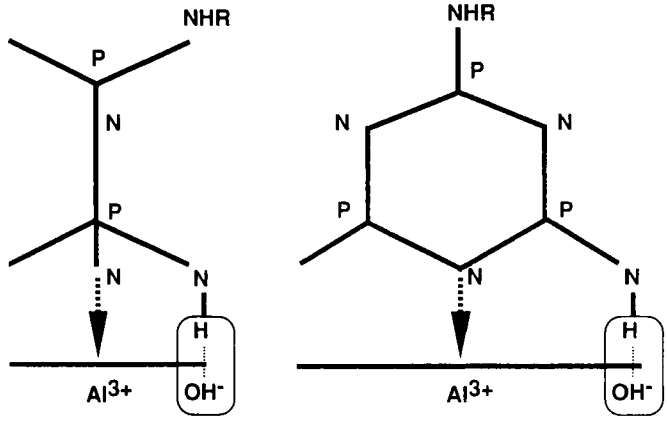

FIGURE 3 Adsorption of a non-gem di-substituted $N_3P_3Cl_4R_2$ on Alumina impregnated with KOH: there exists a strong interaction between N—H bond and dry media. The [N → Al + H···OH^-] bond system is strong enough not to be broken upon elution by toluene.

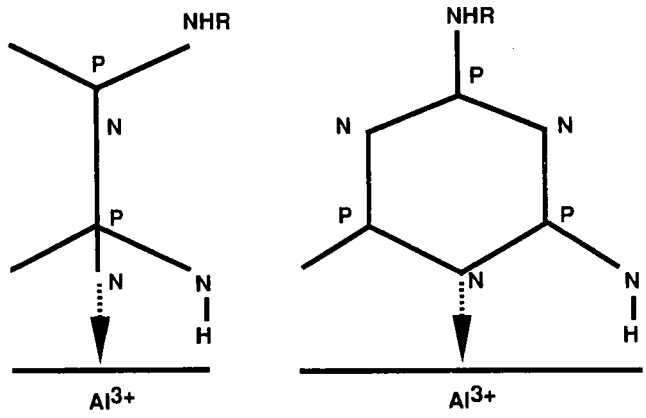

FIGURE 4 Adsorption of a non-gem moiety on non-impregnated Alumina: no interaction between N—H bond and solid support (as in Figure 3). The N → Al dative bond is weak enough to be broken upon elution by toluene.

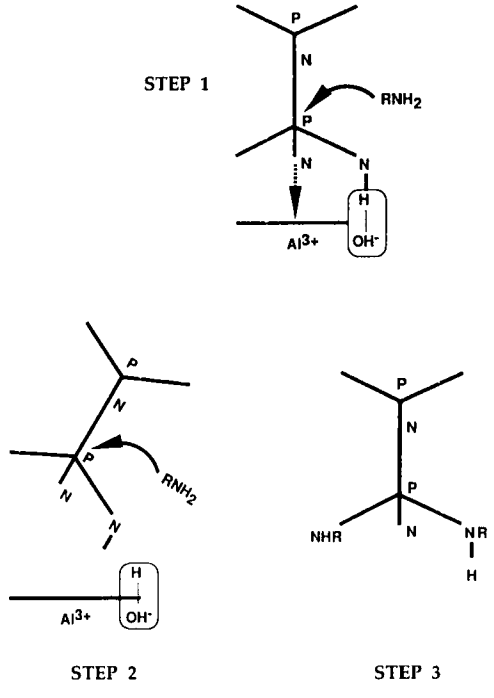

FIGURE 5 Non-adsorption of a gem di-substituted $N_3P_3Cl_4R_2$ on Alumina impregnated with KOH: the proton abstraction process, occurring when the second RNH_2 molecule attacks on the P atom bearing the first amino group, allows elution of the gem moiety.

tion process" (PAP), described by Shaw in 1965[6] and astutely generalized by Allen in 1991,[7] occurs with an abstraction of the proton from the already fixed amino group (making so the molecular system free, i.e. untied from the solid support) and addition of the second RNH_2 in sequence on the free molecular system. In other words, the graft step by step of two amino groups in gem position allows the

elution of these gem moieties in a very facile way whereas the same graft on non-geminal sites leads to firmly adsorbed entities.

Thus, before shuffling the various positive replies we just stated for constructing a general CHEMAC for future, we have still to answer to a fifth (and ultimate at the moment) query: why moisture modifies basically the nature of final products versus the one on carefully dried solid supports?

Up-to-now, we only investigated the effect of moisture when the two starting materials, i.e. $N_3P_3Cl_6$ and octylamine and/or dodecylamine, are deposited simultaneously on the solid support from a common toluene solution. It must be emphasized that, in such conditions, a preliminary reaction occurs immediately in toluene before deposition, leading to the mono-substituted amino derivative, $N_3P_3Cl_5R$ **3** (as demonstrated by "flash" ^{31}P NMR spectroscopy). Then, deposition on (i) dry (i.e. dried for 24 h in oven at 70°C) ALPOT leads to gem derivatives (see above), (ii) dry (i.e. dried for 24 h in oven at 70°C) basic alumina (BASAL) yields non-gem structures while (iii) wet (i.e. no drying in oven) ALPOT and/or BASAL generates non-gem configurations too. Here are the results and their explanation is made obvious from Figure 6 where the presence of water molecules sticked on the surface of the support according to pattern C operates as a sort of chemical shield which inhibits any PAP as in pattern A, leading so to a mechanism basically identical to the one of pattern B. Incidentally, patterns B and C show that the non-gem polysubstituted derivatives obtained in this way must have cis configurations (i.e. **5** or **8**). Indeed, further nucleophilic attacks of RNH_2 molecules on the mono-amino entity **3** as the target will occur preferentially (for obvious steric reasons) on the "upper" side of the N_3P_3 ring, leading consequently to NHR groups grafted on the "lower" side (according to S_N2 mechanisms).

Incidentally, an extra experiment supports nicely this assumption about the role of water: aminolysis of $N_3P_3Cl_6$ by octylamine and/or dodecylamine in (1:1.6) conditions on tiny marbles (diameter 1 to 3 mm) if impregnated with KOH [coded as GLASPOT (50:x)] yields, as expected, gem structures. Indeed, if glassware is superficially covered with layers of moisture which cannot be removed, impregnation with KOH makes a sort of chemical shield which cancels the non-gem effect of moisture and provides so gem configurations.

Now, time is coming to shuffle these "queries and replies" in a general CHEMAC useful for further design of new cyclophosphazenic systems.

A CHEMAC (CHEMICAL MACHINERY) FOR THE AMINOLYSIS OF HEXACHLOROCYCLOTRIPHOSPHAZENE ON SOLID SUPPORTS

The set of queries and replies detailed above can be summarized as follows: 1°—Aminolysis on dry ALPOT yields gem chemicals. Thus, ALPOT may be considered as a selective stationary phase for production of pure gem configurations; 2°—aminolysis on dry BASAL yields non-gem chemicals. Thus, BASAL may be considered as a selective stationary phase for production of pure non-gem configurations; 3°—aminolysis on wet ALPOT and/or BASAL yields non-gem chemicals; 4°—glassware with KOH as solid support (GLASPOT 50:11 and/or 50:33) yields gem chemicals; 5°—aminolysis of $N_3P_3Cl_6$ previously deposited on ALPOT yields

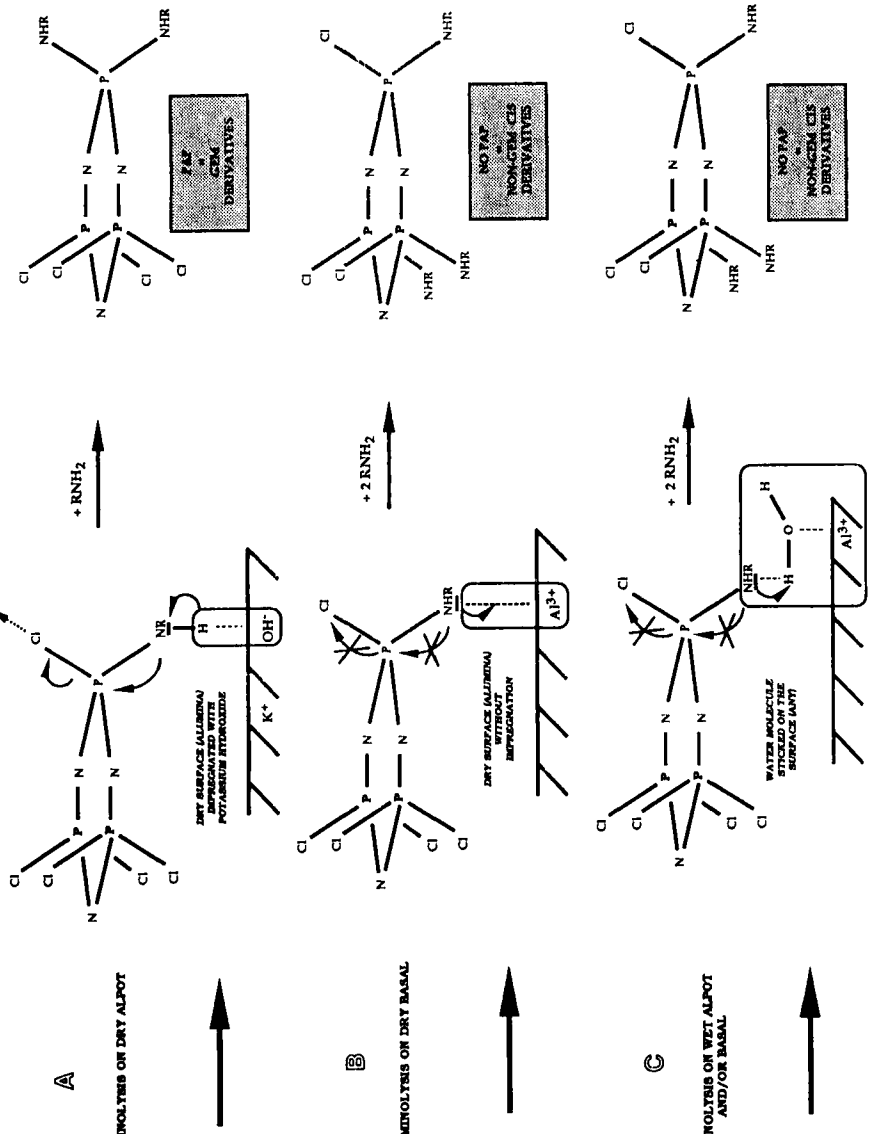

FIGURE 6 Influence of moisture on the nature of configurations for final products.

the hexasubstituted derivative; 6°—finally, whatever the apparently accomplished character of this CHEMAC, we have however to wonder at the fact that the quality of the solid support surface (granulometry, porosity, degree of crystallization) seems to have no influence at all on the actual nature of final products.

EXPERIMENTAL

The NMR spectra were recorded on a Bruker AC 200 spectrometer with H_3PO_4 85% as external reference.

Molecular modelings were achieved by using functionalities of the MAD (Molecular Advanced Design) software developed by Lahana (Oxford Molecular SA, X-Pole, Ecole Polytechnique, 91128 Palaiseau Cedex, France).

Hexachlorocyclotriphosphazene **1** was generously provided to us (degree of purity ≥ 99.8%) by SHIN NISSO KAKO Co, subsidiary company of NIPPON SODA Co. FLUKA supplied us with the primary amines **2** (degree of purity ≥ 98%).

Alumina-supported potassium hydroxide: Potassium hydroxide (Prolabo Rectapur, 11 g) in H_2O (250 ml) was mixed with neutral chromatographic alumina (Fluka, type 207 C, 90–110 μ, 50 g). After stirring for 5 min, the water was removed under reduced pressure. The resulting powder was further dried at 70°C for 24 h in oven. This reagent (coded as ALPOT) may be kept in a desiccator without loss of activity during several months.

Attempt at the synthesis of gem disubstituted moieties upon aminolysis of **1** *by octylamine and/or dodecylamine in homogeneous conditions*: 78 mmol of octylamine in 250 ml of toluene are added dropwise over 2 h at 4°C to a mixture of 39 mmol of **1** and of 140 mmol of Et_3N in 500 ml of the same solvent. The medium is stirred during 7 days till the NMR singlet at 20.1 ppm of **1** has disappeared. Hydrochloride was then filtered off, solvent was removed in vacuo to give a sticky, light yellow powder. The ^{31}P NMR spectrum of the crude final product reveals a medley of several chemicals, namely (i) the expected gem-dioctylamino derivative **4** (triplet centered on 10.3 ppm, doublet centered on 20.3 ppm) (ii) the gem,gem-tetraoctylamino derivative **10** (doublet centered on 12.7 ppm, triplet centered on 22.6 ppm) and (iii) other substituted moieties such as the mono-octylamino entity **3** (triplet centered on 18.5 ppm, doublet centered on 21.7 ppm). According to the relative intensity of NMR peaks, the ratio of these components was 30% for **4** and **10** *versus* 40% for by-products around **3**. Several SiO_2 column chromatographies were found to be unsuccessful for separating **4** from this complex mixture.

General method for the preparation of gem disubstituted moieties **4** *on ALPOT*: A mixture of **1** (2 g; 5.6 mmol) and of the alkylamine (2 Eq.; 11.2 mmol) in toluene (80 ml) was added to ALPOT (40 g corresponding to 10 Eq. of base). After 1 min stirring, the solvent was removed under reduced pressure at room temperature and the resulting white powder was eluted with 2 × 100 ml of toluene or acetone. After removal of the solvent, 2.32 g (76% yield) were obtained which contained mainly **4** with about 10% of **10**. **4** could be purified by a single SiO_2 column chromatography using n-heptane/ethyl acetate (7:3) as the eluant. The NMR spectrum of pure **4** revealed a triplet centered on 10.13 ppm and a doublet centered on 20.34 ppm. Incidentally, the presence of **10** as the impurity suggested to decrease slightly the amount of alkylamine to be used. Actually, a (1:1.6) stoichiometry for the reaction of alkylamines on **1** yields indeed pure **4** straightway (90% yield).

General method for the preparation of hexasubstituted moieties **14** *on ALPOT*: These chemicals might be prepared instantaneously in a pure state through the same way as above but by proceeding through a two-step pathway, i.e. by depositing **1** first and alkylamine next on ALPOT. Hexasubstituted **14** (NMR singlet at 18.29 ppm) were obtained (10% yield) besides unreacted **1** when the (1:1.6) stoichiometry is used but their obtention in a pure state occurred nearly when working in (1:6) stoichiometric conditions.

General remark: The whole results we just described require dried ALPOT (see above). Indeed, if ALPOT is used just as it is at the end of its preparation, i.e. before to be dried at 70°C in oven for 24 h, many non gem by-products are revealed as impurities of the expected gem ones.

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REFERENCES

1. S. Scheidecker, D. Semenzin, G. Etemad-Moghadam, F. Sournies, M. Koenig and J-F. Labarre, *Phosphorus and Sulfur*, **80,** 85 (1993).
2. M. Graffeuil, J-F. Labarre and C. Leibovici, *J. Mol. Struct.*, **22,** 97 (1974).
3. J-P. Bonnet and J-F. Labarre, *Inorg. Chim. Acta*, **149,** 187 (1988).
4. Cf. for example: (a) A. Foucaud, G. Bram and A. Loupy, in "Preparative Chemistry using Supported Reagents," P. Lazlo Ed., Academic Press, Chap. **17,** 317 (1987); (b) G. Bram and A. Loupy, *ibid*, Chap. **20,** 387 (1987); (c) R. Latouche, F. Texier-Boullet and J. Hamelin, *Tetrahedron Lett.*, **32,** 1179 (1991); (d) A. Loupy, G. Bram and J. Sansoulet, *New J. Chem.*, **16,** 233 (1992).
5. G. E. Coxon and D. B. Sowerby, *J. Chem. Soc.*, **A,** 3012 (1969).
6. S. K. Das, R. Keat, R. A. Shaw and B. C. Smith, *J. Chem. Soc.*, 5032 (1965).
7. C. W. Allen, *Chem. Rev.*, **91,** 119 (1991).