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PAPER

Substituent exchange reactions of trimeric and tetrameric aryloxycyclophosphazenes with sodium 2,2,2-trifluoroethoxide

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Substituent exchange reactions of sodium 2,2,2-trifluoroethoxide with trimeric and tetrameric aryloxycyclophosphazenes with phenoxy, 4-formylphenoxy, 4-cyanophenoxy and 4-nitrophenoxy side groups were conducted at 66 °C in THF and monitored by ^{31}P NMR and mass spectrometry. These are model reactions for their counterparts with high polymeric linear organophosphazenes. The ease of displacement of OAr in cyclic trimeric and tetrameric molecules by CF_3CH_2O increased significantly with the presence of electron-withdrawing substituents in the polyphosphazene in the order, phenoxy ≪ 4-formylphenoxy < 4-cyanophenoxy ≈ 4-nitrophenoxy. Fully substituted 2,2,2-trifluoroethoxyphosphazene trimer and tetramer were formed by side group exchange, but these reactions were followed by an attack by the nucleophile on the α-carbon of the 2,2,2-trifluoroethoxy groups linked to phosphorus to give a species in which one trifluoroethoxy group had been replaced by an ONa unit, and bis(trifluoroethyl) ether was formed as a side product. On the other hand, only partly exchanged species were formed when sodium phenoxide reacted with the trifluoroethoxy phosphazene trimer and tetramer, but again a product with an ONa side group was formed eventually together with phenyltrifluoroethyl ether generated *via* alpha-carbon attack. The relative sensitivity of 2,2,2-trifluoroethoxy and phenoxyphosphazene cyclic trimers and tetramers to the presence of trifluoroethoxide was established.

Introduction

Polyphosphazenes are hybrid macromolecules with an essentially linear backbone of alternating phosphorus and nitrogen atoms and with two organic side groups linked to each phosphorus.[1] These polymers have been widely studied for various applications such as bone regeneration scaffolds,[2–4] fire retardants,[5,6] low-temperature elastomers,[7] fuel cell membranes[8–10] and solid or gel polymer lithium ion conductors[11,12] A distinctive feature of polyphosphazenes is the ease with which the polymer properties can be tuned through changes in the side groups.

The most widely explored method for the synthesis of poly(organophosphazenes) is based on the thermal ring-opening polymerization of hexachlorocyclotriphosphazene, $(NPCl_2)_3$, to high polymeric poly(dichlorophosphazene), $(NPCl_2)_n$, followed by the replacement of the labile chlorine atoms in this macromolecular intermediate by organic groups, such as alkoxy, aryloxy, or amino units[13,14] as shown in Scheme 1. In addition, cosubstituted poly(organophosphazenes) can be synthesized by sequential or simultaneous addition of different nucleophiles to conveniently obtain various materials with tunable properties.

However, as mentioned in earlier publicatons,[15–17] an alternative synthesis approach is to replace one organic substituent in the polymer by another using a second organic nucleophile (Scheme 1). This second approach is an appealing alternative, especially for the high polymers since it offers the prospect that single-substitutent poly(organophosphazene)s can be converted readily to mixed-substituent materials which are of broad technological interest. It also raises the possibility that a poly(organophosphazene) that is stable for long periods of time in the atmosphere might be employed as a general macromolecular intermediate for the preparation of other poly(organophosphazene)s. The chloro-derivative intermediate is sensitive to moisture and must be stored under carefully controlled inert conditions. Also, the substitution reactions of the chloro intermediate can only be conducted in a limited number of organic solvents, such as tetrahydrofuran or dioxane.

In addition to its utility for the preparation of new polymers, a systematic study of organic side group exchange reactions can also provide useful information as a practical guide to optimize the classical synthesis of cosubstituted poly(organophosphazenes) prepared by the sequential or simultaneous reactions of two or more nucleophiles with $(NPCl_2)_n$.[18–23] Earlier preliminary work showed that fluorinated alkoxy units[24] and phenoxy side groups can be displaced from polyphosphazenes.[15] For example, for polyphosphazenes that bear both trifluoroethoxy and phenoxy side groups, replacement of phenoxy side groups by 2,2,2-trifluoroethoxide occurs at non-geminally substituted phosphorus atoms. The reverse reaction, exchange of the trifluoroethoxy group

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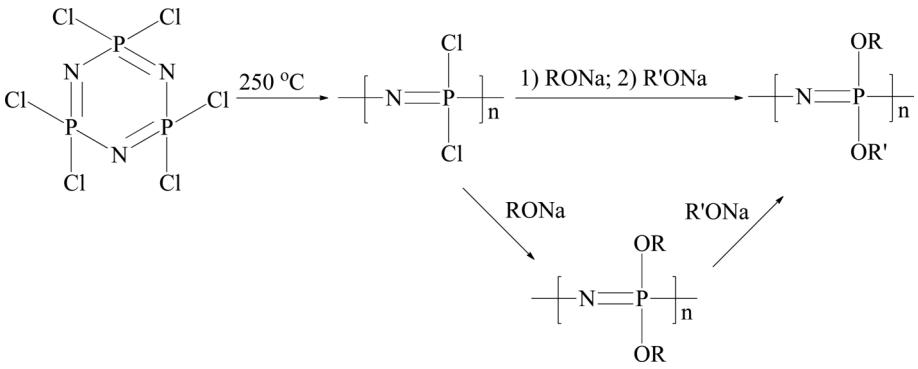


Scheme 1 Synthesis of mixed-substituent poly(organophosphazenes) by Sequential or Simultaneous Addition of Nucleophiles to $(NPCl_2)_n$ or by Side Group Exchange Reactions.

by phenoxide ions, was not detected.[15] Therefore, the order of the sequential addition of different side groups must be considered in order to obtain the desired materials with targeted compositions.

The work presented here is an attempt to examine these processes in more detail. Because the reactions of small molecule cyclic phosphazenes often mimic the behavior of the high polymers, and are easier to analyze, this study is focused on the behavior of cyclic trimeric and tetrameric species. The comparable processes for high polymers will be addressed in a later study.

Experimental

Materials and equipment

All reactions were carried out under an atmosphere of dry argon using standard Schlenk line techniques. Tetrahydrofuran (EMD) was dried using solvent purification columns.[25] 2,2,2-Trifluoroethanol (Aldrich) was purified by vacuum distillation from CaH_2 (Aldrich). Phenol (Aldrich) was purified by sublimation. 4-Nitrophenol was recrystallized twice from toluene. Hexachlorocyclotriphosphazene, $(NPCl_2)_3$, (from various sources including Fushimi Pharmaceutical Co., Japan, and Ningbo Chemical, China) was purified by recrystallization from hexane and by vacuum sublimation at 50 °C. Octachlorocyclotetraphosphazene, obtained from the sublimation residues after the trimer sublimation, was recrystallized twice from toluene and was then vacuum sublimed. Other reagents were used as received. ^{31}P and ^{1}H NMR spectra were obtained with a Bruker 360 WM instrument operated at 145 and 360 MHz, respectively. Spectrometric analysis data were collected using the turbospray ionization technique with use of an Applied Biosystems API 150EX LC/MS mass spectrometer.

Synthesis of cyclic trimeric compounds

Hexakis(2,2,2-trifluoroethoxy)cyclotriphosphazene (***1***). This compound was prepared from $(NPCl_2)_3$ and sodium trifluoroethoxide according to a procedure described previously.[1] Yield: 75.8%. ^{31}P NMR ($CDCl_3$), ppm: δ +17.45 (3P, s). ^{1}H NMR ($CDCl_3$), ppm: δ 4.28 (2H, m, OCH_2CF_3) m/z = 730 ($[M+H]^+$) m/z was calculated for $C_{12}H_{12}F_{18}N_3O_6P_3$.

Hexaphenoxycyclotriphosphazene (***2***). This compound was prepared *via* a procedure reported earlier.[1] Yield: 81.4%. ^{31}P NMR ($CDCl_3$), ppm: δ +9.35 (3P, s). ^{1}H NMR ($CDCl_3$), ppm: δ 6.98, 7.16, 7.23 (5H, m, OC_6H_5) m/z = 694 ($[M+H]^+$) m/z was calculated for $C_{36}H_{30}N_3O_6P_3$.

Hexakis(4-formylphenoxy)cyclotriphosphazene (***3***). The synthesis procedure was reported previously.[26] Yield: 91.2%. ^{31}P NMR ($CDCl_3$), ppm: δ +7.67 (3P, s). ^{1}H NMR ($CDCl_3$), ppm: δ 7.13, 7.72 (4H, d, OC_6H_4CHO), 9.92 (1H, s, OC_6H_4CHO) m/z = 862.4 ($[M+H]^+$) m/z was calculated for $C_{42}H_{30}N_3O_{12}P_3$.

Hexakis(4-cyanophenoxy)cyclotriphosphazene (***4***). Prepared as described previously.[27] Yield: 64.2%. ^{31}P NMR (*d*-DMSO), ppm: δ +7.41 (3P, s). ^{1}H NMR (*d*-DMSO), ppm: δ 7.17, 7.83 (4H, d, OC_6H_4CN).

Hexakis(4-nitrophenoxy)cyclotriphosphazene (***5***). Synthesized *via* a process described earlier.[28] Yield: 82.7%. ^{31}P NMR (*d*-DMSO), ppm: δ +7.30 (3P, s). ^{1}H NMR (*d*-DMSO), ppm: δ 7.31,8.16 (4H, d, $OC_6H_4NO_2$).

Synthesis of cyclic tetrameric compounds

Octakis(2,2,2-trifluoroethoxy)cyclotetraphosphazene (***6***). Prepared as described previously.[14] Yield: 36.1%. ^{31}P NMR ($CDCl_3$), ppm: δ –1.44 (4P, s). ^{1}H NMR ($CDCl_3$), ppm: δ 4.27 (2H, t, OCH_2CF_3). m/z = 973 ($[M+H]^+$) m/z was calculated for $C_{16}H_{16}F_{24}N_4O_8P_4$.

Octaphenoxycyclotetraphosphazene (***7***).[29] Yield: 36.1%. ^{31}P NMR ($CDCl_3$), ppm: δ –11.79 (4P, s). ^{1}H NMR ($CDCl_3$), ppm: δ 6.96, 7.10, 7.17 (5H, m, OC_6H_5). m/z = 925 ($[M+H]^+$) m/z was calculated for $C_{48}H_{40}N_4O_8P_4$.

Octakis(4-formylphenoxy)cyclotetraphosphazene (***8***).[30] Yield: 57.1%. ^{31}P NMR (*d*-DMSO), ppm: δ –13.96 (4P, s). ^{1}H NMR (*d*-DMSO), ppm: δ 7.10, 7.71 (4H, d, OC_6H_4CHO), 9.92 (1H, s, OC_6H_4CHO). m/z = 1149.3 ($[M+H]^+$) m/z was calculated for $C_{56}H_{40}N_4O_{16}P_4$.

Octakis(4-cyanophenoxy)cyclotetraphosphazene (***9***). A mixture of $(NPC1_2)_4$ (1.5 g, 3.2 mmol), 4-cyanophenol (3.6 g, 29.1 mmol) and Cs_2CO_3 (9.5 g, 29.1 mmol) in THF (150 ml), was stirred at reflux for 1 day. The reaction mixture was filtered, and the filtrate was concentrated and precipitated into water. After filtration, the crude **4b** was reprecipitated twice from DMSO into water and twice from DMSO into THF. The product was dried under vacuum to yield 2.96 g of a white solid. Yield: 82.7%. ^{31}P NMR (*d*-DMSO), ppm: δ –14.26 (4P, s). ^{1}H NMR (*d*-DMSO), ppm: δ 7.14, 7.83 (4H, d, OC_6H_4CN).

Octakis(4-nitrophenoxy)cyclotetraphosphazene (***10***), was prepared *via* an earlier procedure.[31] Yield: 70.5%. ^{31}P NMR

(*d*-DMSO), ppm: δ −14.58 (4P, s). ^{1}H NMR (*d*-DMSO), ppm: δ 8.13, 7.26 (4H, d, $OC_6H_4NO_2$)

Purification of $N_3P_3(ONa)(OCH_2CF_3)_5$(***11***). The crude products from the ligand exchange reaction of hexakis(2,2,2-trifluoroethoxy)cyclophosphazene with sodium trifluoroethoxide in THF were dried by rotary evaporation and were redissolved in dichloromethane. After extraction with ammonium chloride (10 wt%) (×3) and deionized water (×3), the organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed by rotary evaporation. A solution of the crude products in a 2 : 1 mixture of dichloromethane and ethyl acetate was passed through a silica gel column prepared using the same solvent. The product was dried under vacuum to give **11**, a yellow liquid. ^{31}P NMR ($CDCl_3$), ppm: δ +18.99, 19.58 (3P, d), 11.71 (2P, t). ^{1}H NMR ($CDCl_3$), ppm: δ 4.28 (2H, m, OCH_2CF_3)

Substituent exchange reactions for both cyclic trimer and tetramer derivatives

All the substituent exchange reactions were carried out in a similar manner. The following is a typical procedure. A solution of **1** (1 g, 1.37 mmol) in THF (10 ml) was added dropwise to a stirred solution of sodium phenoxide (1.91 g, 16.5 mmol) in THF (90 ml). The mixture was stirred at reflux in THF. Typically, reactions were allowed to proceed for up to 50 days. At timed intervals, starting after one day, samples were taken and the reaction progress was monitored by ^{31}P NMR and mass spectrometry. The presence of the etheric side products was established by mass spectrometric analysis of the reaction mixtures.

Results and discussion

The compounds to be discussed are shown in Fig. 1. In the following sections the substituent exchange reactions of **1** and **2** with the nucleophiles, sodium phenoxide and sodium trifluoroethoxide will be discussed first, together with the reactant ratio effects in this system, followed by similar reactions at the cyclic tetramer level (**6** and **7**). In the following section, the use of sodium trifluoroethoxide as the exchange reagent for substituted aryloxycyclophosphazenes will then be described both for the cyclic trimeric (**3**–**5**) and tetrameric systems (**8**–**10**). Finally, the stability of **1**, **2**, **6** and **7** in the presence of excess nucleophile in phosphazene syntheses will be discussed. A summary of the results is given in Table 1.

Reactions of hexaphenoxycyclophosphazene (2) with sodium trifluoroethoxide

Sodium trifluoroethoxide can induce substituent exchange reactions with various aryloxycyclotriphosphazenes, such as hexakis(p-nitrophenoxy)cyclotriphosphazene, hexakis(*o*-nitrophenoxy) cyclotriphosphazene, hexakis(*p*-chlorophenoxy)-cyclotriphosphazene and hexaphenoxycyclotriphosphazene according to an earlier study.[32] It was also reported that, when sodium trifluoroethoxide reacts with **2**, significant amounts of **1** and a large amount of $N_3P_3(OC_6H_5)_3(OCH_2CF_3)_3$ were formed. Very little $N_3P_3(OC_6H_5)_2(OCH_2CF_3)_4$ and almost no $N_3P_3(OC_6H_5)(OCH_2CF_3)_5$ were obtained. However, in this earlier work, the reaction was studied over a relatively short period of time (3 days), and the progress of the entire reaction and identification of the ultimate products were not monitored or examined in detail. Such information is crucial for fully understanding the processes involved in exchange reactions. This is the major issue addressed in this paper.

In this investigation, when hexaphenoxycyclotriphosphazene **2** reacted with sodium trifluoroethoxide in a ratio of 1 : 12 at reflux temperature (66 °C) in THF, hexakis(2,2,2-trifluoroethoxy)cyclophosphazene (**1**) is generated by a substituent exchange reaction. This product was detected by ^{31}P NMR spectrometry after two days of reaction (Fig. 2b) together with a second phosphazene product (**11**) (doublet-triplet, 19.9 ppm and 11.1 ppm). This second product was also formed in other substituent exchange reactions and will be discussed later. The amounts of both products **1** and **11** increased as the reaction progressed and as the starting material, **2**, was consumed. After 50 days reaction, no further change of the ratio in the components in the reaction was detected, which indicated that the interaction had reached a steady state. At this stage the percentage of each phosphazene component in the reaction mixture was **2** 16.9%, **1** 10.8% and **11** 72.3% (Fig. 2d).

The reaction rate and ratios of the products were significantly dependent on the concentration of the nucleophile. The rate of consumption of **2** under reaction conditions *b* (Table 1) was much faster than under conditions *a* as the amount of trifluoroethoxide was doubled. Thus, after 50 days reaction, the starting material **2** was almost completely consumed (reaction conditions *b* and Fig. 3d). Furthermore, the higher concentration of trifluoroethoxide caused a greater tendency for **1** to be transformed to side product **11** (Fig. 4b).

The absence of partly exchanged products from reactions carried out under these conditions suggests that the reaction

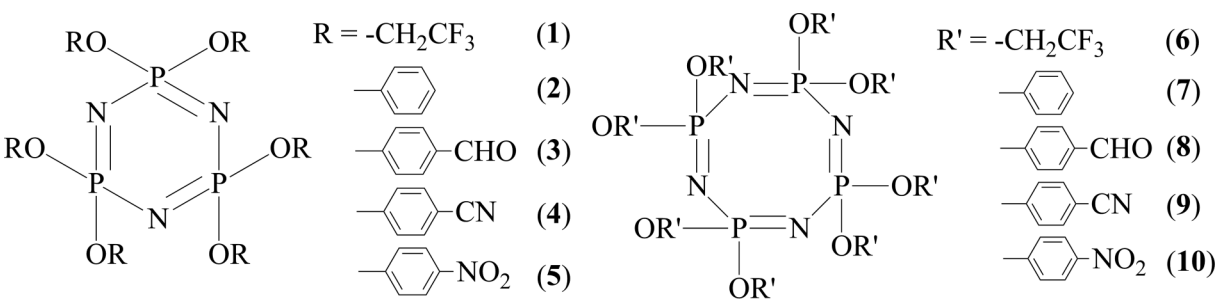
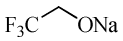
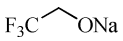
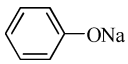
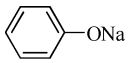
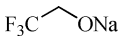
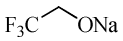
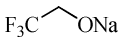
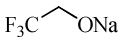
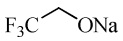
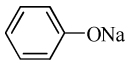
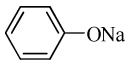
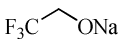
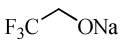
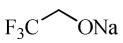
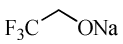
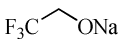
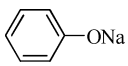
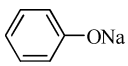


Fig. 1 Structures of cyclic trimeric and tetrameric phosphazenes.

Table 1 Reaction conditions and major products

Reaction	Initial phosphazene	Nucleophile	Molar ratio of phosphazene : nucleophile	Major products
a	**2**		1 : 12	**1**, **11b**
b	**2**		1 : 24	**1**, **11**
c	**1**		1 : 12	**11**, **12**
d	**1**		1 : 24	**11**, **12**
e	**3**		1 : 12	**1**, **11**
f	**4**		1 : 12	**1**, **11**
g	**5**		1 : 12	**1**, **11**
h	**7**		1 : 12	**6**, **13**, **14**
i	**7**		1 : 24	**6**, **13**, **14**
j	**6**		1 : 12	**13**, **14**, **15**
k	**6**		1 : 24	**13**, **14**, **15**
l	**8**		1 : 12	**6**, **13**, **14**
m	**9**		1 : 12	**6**, **13**, **14**
n	**10**		1 : 12	**6**, **13**, **14**
o	**1**		1 : 12	**11**
p	**6**		1 : 12	**13**
q	**2**		1 : 12	—
r	**7**		1 : 12	—

[a] **1** = $N_3P_3(OCH_2CF_3)_6$; **2** = $N_3P_3(OC_6H_5)_6$; **3** = $N_3P_3(OC_6H_4CHO\text{-}p)_6$; **4** = $N_3P_3(OC_6H_4CN\text{-}p)_6$; **5** = $N_3P_3(OC_6H_4NO_2\text{-}p)_6$; **6** = $N_4P_4(OCH_2CF_3)_8$; **7** = $N_4P_4(OC_6H_5)_8$; **8** = $N_4P_4(OC_6H_4CHO\text{-}p)_8$; **9** = $N_3P_3(OC_6H_4CN\text{-}p)_6$; **10** = $N_3P_3(OC_6H_4NO_2\text{-}p)_6$; [b] **11** = $N_3P_3(OCH_2CF_3)_5(O^-Na^+)$; **12** = $N_3P_3(OCH_2CF_3)_5(OC_6H_5)$; **13** = $N_4P_4(OCH_2CF_3)_7(O^-Na^+)$; **14** = $N_4P_4(OCH_2CF_3)_6(O^-Na^+)_2$; **15** = $N_4P_4(OCH_2CF_3)_{8-x}(OC_6H_5)_x$ (x = 1 ~ 4).

proceeds as a self-accelerating process due to the strong electron-withdrawing effect of trifluoroethoxy side groups. This electron-withdrawal renders the cyclophosphazene more susceptible to further attack by the nucleophile.

Side product 11

Side product **11** was shown by ^{31}P NMR and mass spectrometry to have the structure shown in Scheme 2. The mass spectral identification was accomplished using a negative model mass spectrometer under a neutral mobile phase (acetonitrile) to give a mass of 645.9, which matches the structure shown in Scheme 2.

This product is formed from **1**, itself generated by side group exchange from **2**. Evidence in favor of this interpretation is as follows. (a) No partially exchanged phenoxy-trifluoroethoxy cyclic phosphazenes were detected by mass spectrometry for these reaction conditions: only the fully exchanged cyclophosphazene **1** was present. (b) There is a parallel increase in the formation of **1** and **11** as the reaction proceeds. (c) No products similar to **11** but containing phenoxy groups were detected in any of these reactions.

The mechanism shown in Scheme 2 supposes that trifluoroethoxide ion participates in a nucleophilic attack on the alpha-carbon atom of a side group in **1**. Two factors favor the view that the main attacking species is trifluoroethoxide rather than

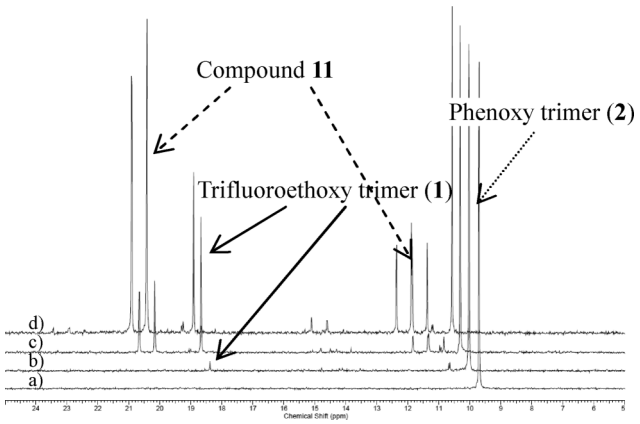


Fig. 2 ^{31}P NMR spectra for the reaction between **2** and sodium trifluoroethoxide (molar ratio 1 : 12) a) 2 h; b) 2 days; c) 16 days; d) 50 days.

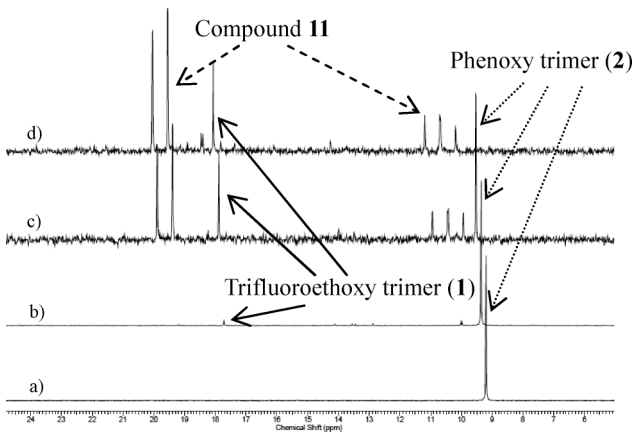


Fig. 3 ^{31}P NMR spectra for reaction between **2** and sodium trifluoroethoixde (molar ratio 1 : 24) a) 2 h; b) 1 day; c) 30 days; d) 50 days.

phenoxide. First, in a separate reaction between **1** and sodium trifluoroethoxide, the etheric side product $CF_3CH_2OCH_2CF_3$ was identified by mass spectrometry (mass = 163.01). Second, in the reaction between **2** and sodium trifluoroethoxide, the concentration of trifluoroethoxide is always higher than phenoxide even at the end of the side group exchange process.

Reactions of hexakis(2,2,2-trifluoroethoxy)phosphazene (1) with sodium phenoxide

The reverse reaction is less facile than the one discussed above. No hexaphenoxycyclophosphazene (**2**) was detected in the substituent exchange reactions between **1** and sodium phenoxide at a ratio 1 to 12 (reaction conditions *c*) or 1 to 24 (conditions *d*). Only the mono-exchanged derivative, $N_3P_3(OCH_2CF_3)_5OPh$ (**12**), and side product **11** (Fig. 5) were detected. Both reactions reached a steady state after 10 and 25 days respectively. (Fig. 6) From the mass spectra, the final products from reaction conditions *c* and *d* were compounds **11** and **12** (Scheme 3), which suggests that the two products were formed through different pathways.

The reason why no fully exchanged product, hexaphenoxycyclophosphazene, (**2**), was detected is probably due to the higher steric hindrance characteristic of phenoxide units and the lower

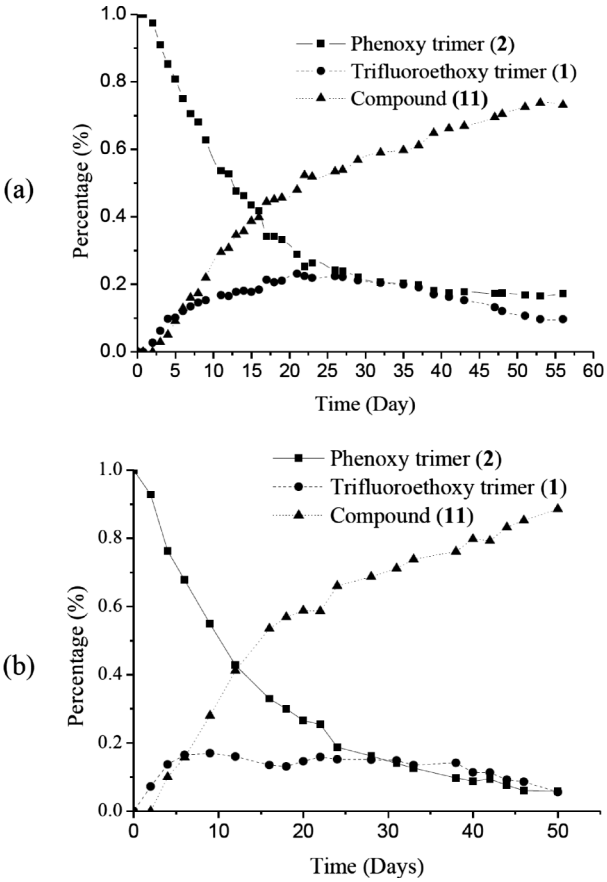


Fig. 4 Reactions of hexaphenoxycyclotriphosphazene (**2**) with sodium trifluoroethoxide: molar ratio a) 1 : 12; b) 1 : 24.

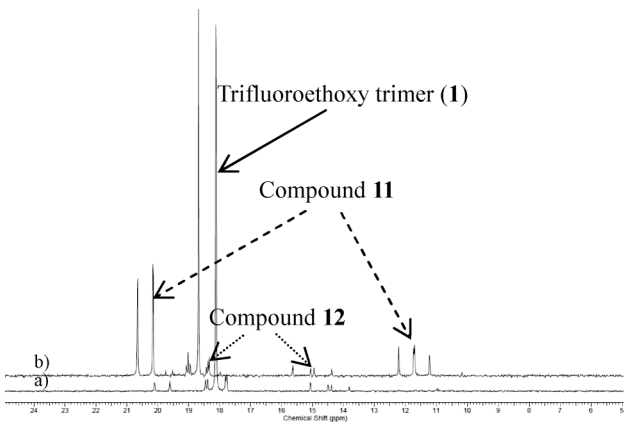
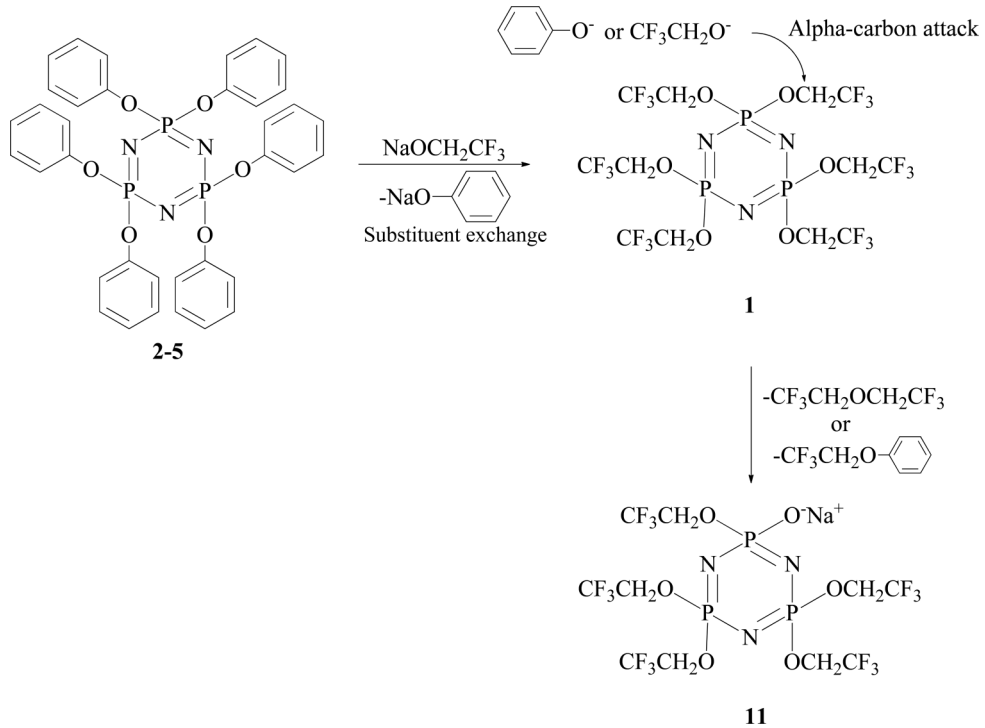


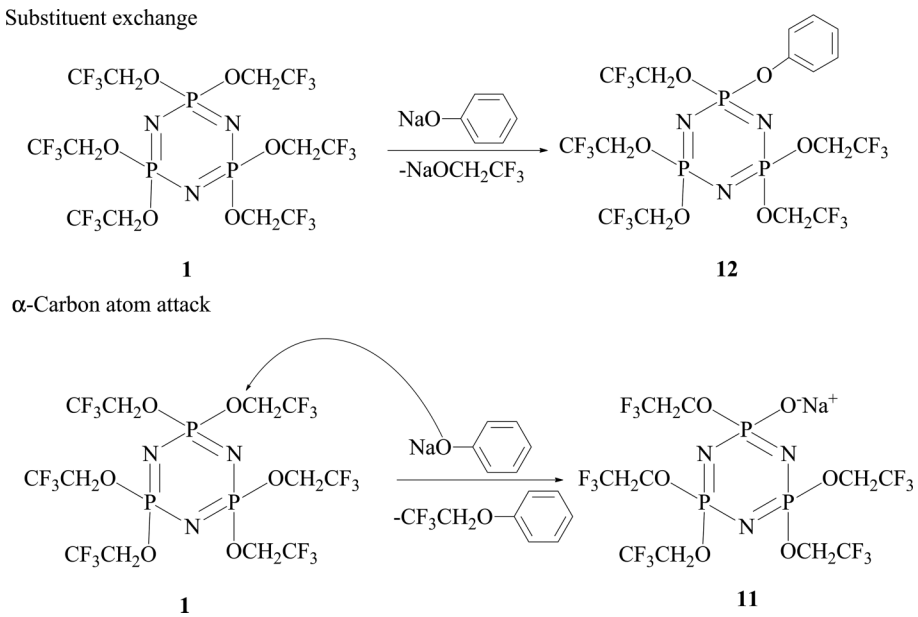
Fig. 5 ^{31}P NMR spectra for substituent exchange reaction between **1** and sodium phenoxide for 2 days: molar ratio a) 1 : 12; b) 1 : 24.

nucleophilicity which make it difficult to achieve full replacement of trifluoroethoxy groups.

Thus, the smaller and more nucleophilic trifluoroethoxide ion can replace larger phenoxy groups to lower the overall steric restrictions around phosphorus, but the reverse process is more restricted. Therefore, although this exchange reaction is reversible, it relies significantly on the preferred production of **1**. Meanwhile, **1** is still liable to be attacked by a nucleophile (either phenoxide or trifluoroethoxide) at the α-carbon of the alkoxy side unit to generate side product **11**. The mass spectrometric identification of



Scheme 2 Two step pathway involved in the formation of compound **11**.



Scheme 3 Two separate processes leading to the formation of **11** and **12** during the reaction of sodium phenoxide with hexakis(2,2,2-trifluoroethoxy)cyclotriphosphazene (**1**).

trifluoroethylphenyl ether (mass = 176.02) as a reaction product from the interaction of **1** with sodium phenoxide is further evidence for the process shown.

On the other hand, the final products from reaction conditions *c* and *d* also depended on concentration as with conditions *a* and *b*. In the initial stage, condition *d* induced a much higher reactivity than did condition *c*. For example, 23.3% of the starting material (**1**) was consumed under conditions *c* after two days (Fig. 6a). By contrast, 58.3% of **1** had reacted with sodium phenoxide under conditions *d* (Fig. 5b). Furthermore, when the interactions reached their steady state, only small amounts of compounds **11** and **12** were generated under conditions *c*. Most of the starting material **1** remained intact (Fig. 6a). However, when twice the amount of sodium phenoxide was used (condition *d*), a significant

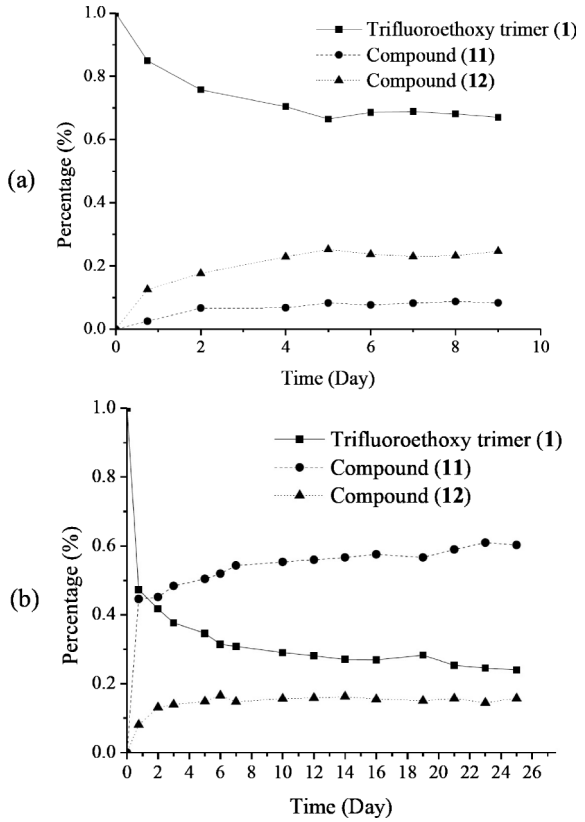
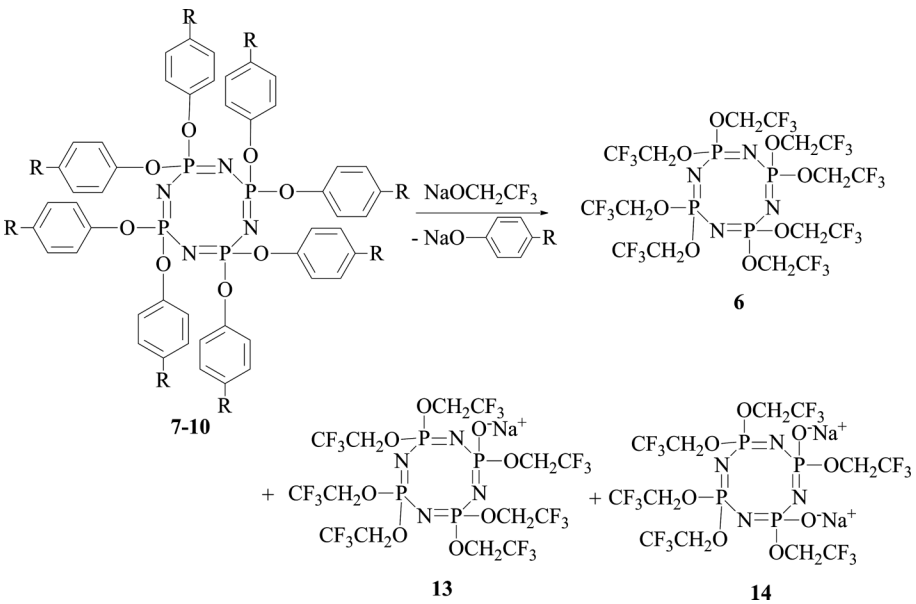


Fig. 6 Reactions of hexakis(2,2,2-trifluoroethoxy)cyclotriphosphazene (**1**) with sodium phenoxide: molar ratio a) 1 : 12; b) 1 : 24.

amount of compound **11** was generated, with roughly 75% of **1** consumed in the end (Fig. 6b). This showed that hexakis(2,2,2-trifluoroethoxy)cyclophosphazene is more prone to attack by the nucleophile as the concentration of the phenoxide increases, which follows the same tendency as the results obtained for conditions *a* and *b*.

Reactions at the cyclic tetrameric level: octaphenoxycyclophosphzene (7) with sodium trifluoroethoxide

As in the cyclic trimer reactions, in the tetrameric system, octakis(2,2,2-trifluoroethoxy)cyclophosphazene (**6**), was produced through substituent exchange reactions between octaphenoxycyclophosphazene (**7**) and sodium trifluoroethoxide, but at a much faster rate. The side products **13** and **14** were detected by ^{31}P NMR and confirmed by mass spectra. Again, reactions took place through the pathways shown in Scheme 4. However, the faster reaction rate at the cyclic tetramer level was illustrated by the following observation: in the cyclic trimer system, the starting material **2** could still be detected by ^{31}P NMR spectrometry after one month (reaction conditions *a* and *b*), but in the cyclic tetramer system, most of the starting material **7** had been converted to **6**, together with compounds **13** and **14** within 3 days with only 7.7% and 1.8% of starting material **7** remaining (conditions *h* and *i* and Fig. 7). These effects may reflect the greater flexibility of the larger ring and the resultant greater exposure of the phosphorus atoms to nucleophilic attack, due to the more open structure and lower steric hindrance compared to the cyclic trimer.[1] It also suggests that this effect could be even more evident at the high polymer level. In addition, recent calculations show that the formal positive charge on phosphorus is greater in the tetramer *vs.* the trimer which is another likely source of the greater rate of reaction in the tetramer. Actually, the trimer/tetramer results presented here are consistent with the effects found for other related reactions. Thus, the rate of exchange of chloride ion in $(NPCl_2)_4$, is faster than in $(NPCl_2)_3$.[33] Hydrolysis of $(NPCl_2)_4$ or $(NPF_2)_4$, proceeds faster than the hydrolysis of $(NPC1_2)_3$ or $(NPF_2)_3$.[34,35] Also, aminolysis of $(NPCl_2)_4$ takes place more rapidly than the reaction of $(NPC1_2)_3$,[36] and the degradation of cyclophosphazenes to phosphoranes in the



Scheme 4 Products from the reactions between aryloxy tetramers (**7–10**) and sodium trifluoroethoxide.

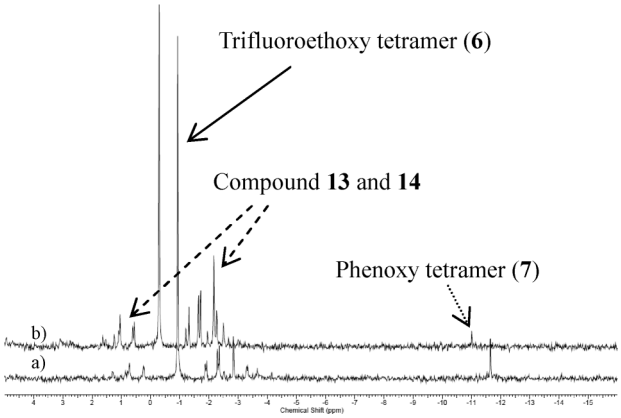


Fig. 7 ^{31}P NMR spectra for substituent exchange reaction between **7** and sodium trifluoroethoxide for 3 days: molar ratio a) 1 : 16; b) 1 : 32.

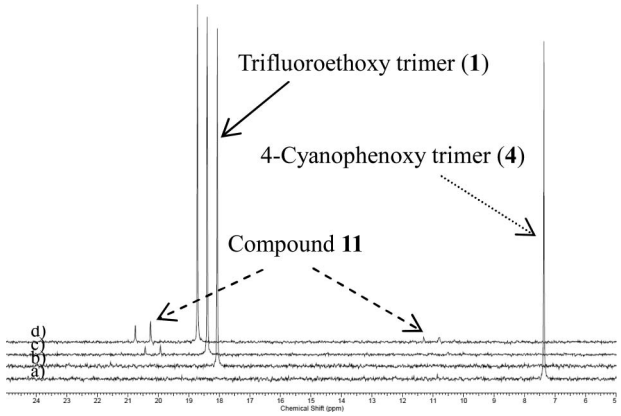


Fig. 8 ^{31}P NMR spectrum for substituent exchange reaction between **4** and sodium trifluoroethoxide for: a) 0 h; b) 0.5 h; c) 4 h; d) 1 day.

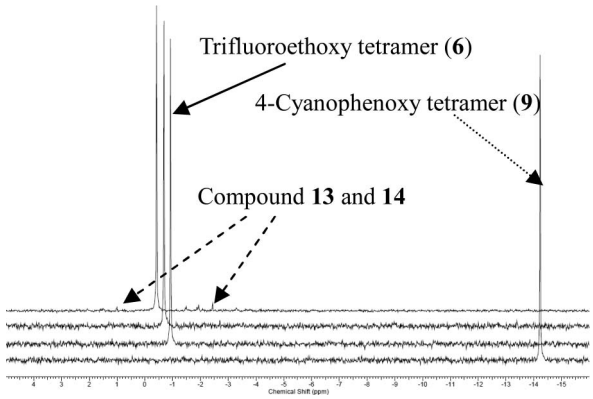


Fig. 9 ^{31}P NMR spectra for substituent exchange reaction between **9** and sodium trifluoroethoxide for: a) 0 h; b) 0.5 h; c) 4 h; d) 1 day.

presence of catechol or o-phenylenediamine occurs more readily with cyclic tetramers than with trimers.[37,38]

Reactions of octakis(2,2,2-trifluoroethoxy)cyclophosphazene (6) with sodium phenoxide

The reverse exchange reaction at the cyclic tetramer level (reactions *j* and *k*) gave results similar to their cyclic trimeric counterparts. No octaphenoxycyclophosphazene (**7**) was generated in either reaction after 22 days, and only partially-substituted $N_4P_4(OCH_2CF_3)_{8-x}(OC_6H_5)_x$ (**15**) species were identified by mass spectrometry. The value of x can be from 1 to 4. Furthermore, the side product **13** appeared after 5 days reaction, showing that the α-carbon attack on the side group by the nucleophile also took place in these reactions.

Reactions of 3, 4, 5 and 8, 9, 10 with sodium trifluoroethoxide

In all of these side group exchange reactions fully-substituted hexakis(2,2,2-trifluoroethoxy)cyclophosphazene (**1**) or octakis(2,2,2-trifluoroethoxy)cyclophosphazene (**6**) were generated by side group exchange. This is similar to the results discussed above for reactions *a* and *h*. However, a much faster exchange reaction rate occurred with these substituted aryloxycyclotetraphosphazene than with the parent phenoxyphosphazenes. The replacement reaction proceeds much faster because of the electron-withdrawing substituent groups on the aryl rings. This renders the skeleton more electron-deficient and more liable to attack by nucleophiles. This assumption was confirmed by the reactions of cyclic trimers and tetramers with 4-formylphenoxy (**3** and **8**), 4-cyanophenoxy (**4** and **9**) and 4-nitrophenoxy (**5** and **10**) side groups with sodium trifluoroethoxide. As shown in Table 2, within half an hour, hexakis(2,2,2-trifluoroethoxy)cyclophosphazene (**1**) or octakis(2,2,2-trifluoroethoxy)cyclophosphazene (**6**) were formed by substituent exchange reactions and were detected by ^{31}P NMR spectrometry. This same process would require 1 or 2 days for hexaphenoxycyclophosphazene (**2**) and octaphenoxycyclophosphazene (**7**). Moreover, all of the starting materials were consumed within half an hour, except in the case of 4-formylphenoxy trimer (**3**) (2 h). Again, this is much faster than the analogous reactions of hexaphenoxycyclophosphazene (**2**) and octaphenoxycyclophosphazene (**7**) with sodium trifluoroethoxide (reactions *a* and *b*). Taking 4-cyanophenoxy trimer as an example, as shown in Fig. 8, all of the starting material (hexakis(4-cyanophenoxy)cyclophosphazene, **4**) was converted to **1** within 30 min without the appearance of any detectable side product **11**. However, after 4 h, compound **11** was detected and increased in concentration as the reaction proceeded. Similar results at the cyclic tetramer level between octakis(4-cyanophenoxy)cyclophosphazene (**9**) and sodium trifluoroethoxide were also obtained, as seen in Fig. 9. This process is quite similar to that of its cyclic trimeric counterpart (**4**). Therefore, the assumption proposed at the beginning of this section was reinforced by the results obtained in these reactions. Thus, the replacement reactivity was dramatically increased due to the electron-deficiency within the cyclic trimeric or tetrameric rings.

Stability of 1, 2, 6 and 7 in the presence of nucleophiles

Compounds **11**, **13** and **14** always appeared during different substituent exchange reactions, which indicated a relatively high sensitivity of both hexakis(2,2,2-trifluoroethoxy)-cyclophosphazene (**1**) and octakis(2,2,2-trifluoroethoxy)-cyclophosphazene (**6**) under these reaction conditions. Actually, it has been shown that fluoroalkoxycyclophosphazenes,[39] aryloxy- and spiroarylenedioxycyclophosphazenes[28] undergo hydrolysis in basic aqueous media. Hexakis(2,2,2-trifluoroethoxy)cyclophosphazene can be hydrolyzed in solution by aqueous alkali, undergoing nucleophilic attack by hydroxide

Table 2 Reaction time of aryloxy trimer and tetramer derivatives with sodium trifluoroethoxide

	Trimers					Tetramers		
	2	**3**	**4**	**5**	**7**	**8**	**9**	**10**
t_1[a]	2 d[d]	0.5 h[d]	0.5 h	0.5 h	1 d	0.5 h	0.5 h	0.5 h
t_2[b]	—	2 h	0.5 h	0.5 h	7 d	0.5 h	0.5 h	0.5 h
t_3[c]	3 d	1 d	4 h	1 h	2 d	3 d	1 d	18 h

[a] Time for the appearance of **1** or **6**. [b] Time for complete consumption of starting material. [c] Time for the appearance of **11** or **13** and **14**. [d] d: day, h: hour.

ion at phosphorus *via* an S_N2-type mechanism through a nongeminal pathway.[39] Such a mechanism allows retention of the ~120° N–P–N ring angle during formation of a trigonal-bipyramidal transition state. Moreover, the initial product formed during the hydrolysis of **1** is believed to be **11**. Cyclic tetramers behave similarly, but with two- to four-fold faster hydrolysis rates, which can be explained by the reasons discussed above. Care was taken to exclude water from all the reactions described here, and it can be assumed that the attacking species is trifluoroethoxide rather than hydroxide. A similar cleavage mechanism and products have also been detected from the reaction of excess nucleophile with heterophosphazenes by Manners *et al.*[40]

Nevertheless, a key reaction to supplement the side group exchange studies is the interaction of hexakis(2,2,2-trifluoroethoxy)cyclophosphazene (**1**) with sodium trifluoroethoxide (molar ratio 1 : 12) under the same reaction condition as in all the other reactions. As shown in Fig. 10, the side product **11**, appeared after one day of reaction, even though initially it constituted less than 2% of the product mixture. As the reaction proceeded, **1** was gradually converted to compound **11** and no other products were detected. After 41 days, approximately 90% of **1** had been converted into **11**. Moreover, as mentioned earlier, chemical ionization mass spectrometric analysis of the reaction mixture revealed the presence of bis(trifluoroethyl) ether (mass 163.01), which is the other side product consistent with the proposed mechanism. These experiments indicate the sensitivity of hexakis(2,2,2-trifluoroethoxy)cyclophosphazene (**1**) when exposed to a large excess of a nucleophile under normal synthetic conditions. Thus, attention should be paid to this aspect when synthesizing small molecules or even high polymers to limit the exposure time of the final products to an excess of the nucleophile to prevent the generation of the undesired side product.

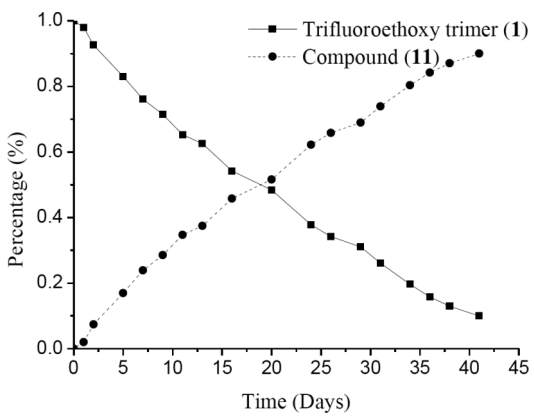


Fig. 10 Formation of species **11** from the reaction of **1** with sodium trifluoroethoxide: molar ratio 1 : 12.

By contrast, no side product was detected from the reactions of hexaphenoxycyclophosphazene (**2**) or octaphenoxycyclophosphazene (**7**) with sodium phenoxide under exchange reaction conditions after one week. This illustrates the ability of **2** and **7** to resist nucleophilic attack, and may reflect the excellent protection of the backbone by bulky phenoxy groups especially to nucleophilic attack by sodium phenoxide. It may also be connected with the absence of a bridging CH_2 group, which would enhance the conformational flexibility of both the polymer and the nucleophile and deprive the system of a site for alpha-carbon attack.

Conclusions

The side group exchange reactions of cyclic trimeric and tetrameric aryloxycyclophosphazenes with sodium 2,2,2-trifluoroethoxide are dependent on the electron-withdrawing effects of different side groups. The ease of displacement of OAr in cyclic trimeric and tetrameric molecules by $CF_3CH_2O^-$ increased significantly in the order, OAr = phenoxy ≪ 4-formylphenoxy < 4-cyanophenoxy ≈ 4-nitrophenoxy derivatives. In addition, the side product generated *via* the attack by the nucleophile on the α-carbon of the 2,2,2-trifluoroethoxy group was detected in all the exchange reactions after 2,2,2-trifluoroethoxy phosphazene trimer or tetramer had been formed. The cyclic phenoxyphosphazene trimer and tetramer showed significantly better stability in the presence of sodium phenoxide than did the 2,2,2-trifluoroethoxy trimer or tetramer.

The information obtained here is valuable as a model study for the synthesis of phosphazene high polymers. As in the cyclic trimer or tetramer, the α-carbon of the fluoroalkoxy side groups in the corresponding high polymeric phosphazenes may also be liable to attack by excess nucleophilic reagents in the reaction solution, ultimately generating products with low molecular weights. These results are also significant in view of the report by Ferrar *et al.* that the reaction of excess sodium trifluoroethoxide with $(NPCl_2)_n$ leads to lower molecular weight trifluoroethoxyphosphazene polymers.[41] Furthermore, reaction of poly[bis(trifluoroethoxy)phosphazene] with excess sodium trifluoroethoxide also resulted in the transformation of a crystalline polymer to an amorphous one. This result coincides with changes in DSC thermograms, optical micrographs, and ^{31}P NMR spectra, that suggest a secondary reaction by sodium trifluoroethoxide on the polymer.

The work reported here is also important with respect to the order in which nucleophiles should be added to high polymeric $(NPCl_2)_n$ to obtain specific mixed-substituent side group ratios and

avoid both side group exchange and the formation of side products similar to **11**. In order to understand these aspects in more detail, comparable reactions of short chain linear phosphazenes and high polymers are currently underway.

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