Lack of Co-crystal Formation with Cyclotriphosphazenes: A Cautionary Tale†

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ABSTRACT

The attempted formation of co-crystals with a series of cyclotriphosphazene derivatives has been investigated. Despite numerous attempts, only one co-crystal was obtained. The crystal structure of this material, [hexakis(4-pyridyloxy)-cyclotriphosphazene][terephthalic acid]$_{2.5}$, is presented here. The crystal structures of 2,2-bis(4-formylphenoxy)-4,4,6,6-bis[spiro(2′,2″-dioxy-1′,1″-biphenylyl]cyclo-triphosphazene and hexakis(4-cyanophenoxy)cyclotriphosphazene are also reported for the first time. The extremely low rate of co-crystal occurrence in these materials cannot be explained, despite the consideration of several possibilities. This serves as a cautionary tale – co-crystal formation is not necessarily straightforward.

KEYWORDS

Cyclophosphazene, lack of co-crystal formation.

1. Introduction

Cyclophosphazenes, which are formally unsaturated compounds containing alternating phosphorus-nitrogen bonds,[1] have received much attention due to the wide range of possible applications for these compounds.[2] Cyclotriphosphazenes, $(R_2PN)_3$, have received particular attention from the crystal engineering community since the discovery of the remarkable inclusion properties of tris(*o*-phenylenedioxy)cyclotriphosphazene (TPP).[3] TPP is a highly robust host, forming inclusion complexes in the solid state with a variety of solvents, whether it is exposed to liquids or to solvent vapours.[4] The high density, nonporous structure of TPP has also been determined, and it has been shown that under CO_2 pressure the high density structure can be transformed to the low density, porous structure.[5] Not only does this particular organic host include a wide variety of small organic molecules, but it has also been shown to include various polymers.[6] We speculated that if TPP has the ability to form such a broad range of inclusion compounds, the possibility exists that other cyclotriphosphazene derivatives could also form a range of interesting supramolecular assemblies – be they inclusion compounds or co-crystals.[7] It was therefore decided to embark on a systematic investigation of co-crystal and solvate formation with various cyclotriphosphazene derivatives.

Cyclotriphosphazenes are attractive targets for this kind of systematic study due to the ease of synthesis of a variety of substituted derivatives from hexachlorocyclotriphosphazene, $(NPCl_2)_3$.[2a,4c,8] Despite this, there have been few systematic crystal engineering studies on cyclotriphosphazenes.[9] Chandrasekhar *et al.*[9a] used cyclotriphosphazenes and the principles of directional hydrogen bonding to design supramolecular assemblies in the solid state. They specifically selected hydrazide derivatives with the intent of using the terminal $–NH_2$ groups as proton donors and the phosphazene ring nitrogen atoms as proton acceptors. This interaction results in the formation of a hexagonal close-packed sheet in the case of $N_3P_3[N(Me)NH_2]_6$. When one of the phosphorus atoms is substituted with a 2,2′-biphenol group – *spiro*-$N_3P_3[O_2C_{12}H_8][N(Me)NH_2]_4$ – it results in the formation of a double chain through the hydrogen bonding of a ring nitrogen atom to a $N(Me)NH_2$ substituent. This is one of the few examples of using tailored intermolecular interactions to direct the aggregation of cyclotriphosphazenes.

There are also a number of known co-crystals containing a cyclotriphosphazene derivative.[10] One of the most interesting co-crystals is that of hexakis(4-carboxyphenoxy)-cyclotriphosphazene with hexakis(4-pyridylcarbinoxy)cyclotriphosphazene (CSD refcode EZEJEY).[11,12] Hydrogen bonds are formed between the carboxylic acid and pyridyl groups on the cyclotriphosphazenes. Due to the three-up and three-down arrangement of the substituents on each cyclotriphosphazene, they assemble to form columns in the crystal structure. Halogen bonding between iodo-substituted perfluorocarbons and pyridyl moieties has been successfully used to construct co-crystals of cyclotriphosphazenes.[10a,b] One of these co-crystals also forms a pillared structure due to the arrangement of the cyclotriphosphazene substituents.[10b] These co-crystals served as the inspiration to design similar pillared assemblies with different cyclotriphosphazene derivatives.

We selected a number of substituted cyclotriphosphazenes (Scheme 1) that have either the potential to form strong supramolecular synthons (hydrogen or halogen bonds), or have awkward shapes, or both. We hoped that the flexibility and awkward shape of these molecules in general might predispose them to crystallize as solvates in the solid state. The co-formers that were selected had the potential to form known supramolecular synthons with the functional groups on the phosphazenes (hydrogen bonds, halogen bonds, π–π interactions).

At the start of this investigation, it was anticipated that several co-crystals would be obtained. Molecules and co-crystal formers with the potential to form strong supramolecular synthons were selected, and a thorough screen was planned. In general, publications involving co-crystal synthesis do not report problems encountered in obtaining co-crystals. A close look at the most recent papers in a top crystal engineering journal[13] containing

† We dedicate this paper to the many postgraduate students we have met over the past few years who despair of ever getting a co-crystal. You are not alone.

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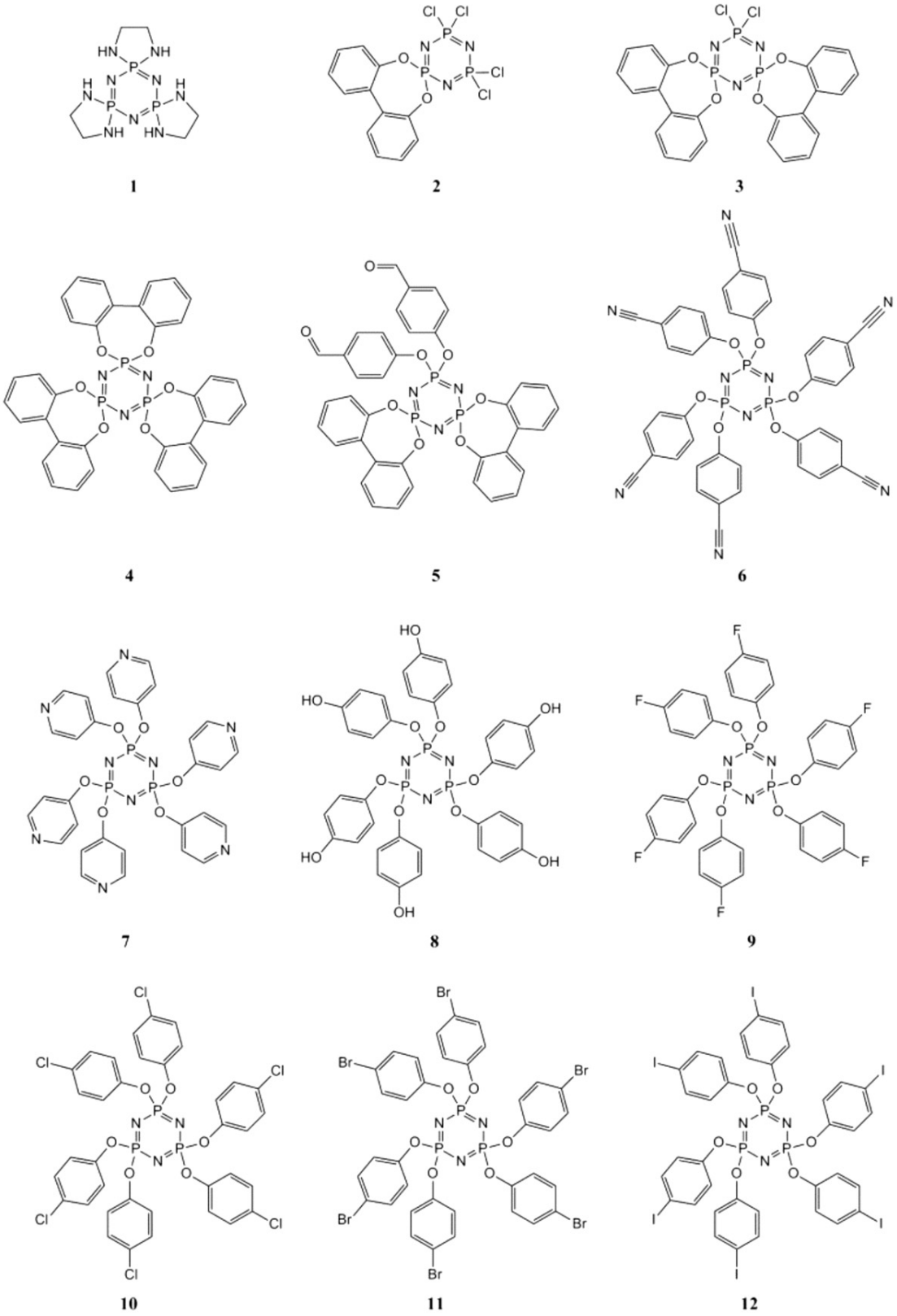

Scheme 1
The cyclotriphosphazene derivatives investigated in this study.

the word co-crystal (or cocrystal) in the title confirms this. One of the studies discusses salt *versus* co-crystal formation, and it appears multi-component crystals were obtained for all combinations investigated.[13c] Four of the studies involve co-crystal screens. In one screen it seems all combinations tried gave co-crystals.[13a] In the other three screens, co-formers were chosen so as to form strong intermolecular interactions. Two screens had low rates of co-crystal formation (1 co-crystal from 8 combinations[13b] and 4 co-crystals from 25 combinations[13e]), but make no comment on this. The third screen found 4 co-crystals from around 300 crystallizations.[13d] The researchers comment 'The scarcity of co-crystals of fenamic acid derivatives, as reported in

this study and in previous literature, is due to both the strong carboxylic acid homodimer synthon that is dominant within the numerous polymorphs of the fenamic acid derivatives, and the ability for the molecules to adopt several stable conformations of their own. The strength of these interactions within these systems results in the evident preferential formation of polymorphs over co-crystals.'

Some groups have reported investigations into why certain co-crystals (or groups of co-crystals) do not readily form; however, these papers are few and far between.[14] From the literature, a newcomer to this field might expect that obtaining a co-crystal is a relatively simple matter – as long as an appropriately strong interaction could form between the two co-crystal formers, a co-crystal will be isolated. The results of our extensive study, reported herein, show that this is most certainly not always the case.

2. Experimental

Cyclophosphazenes **1**–**12** were synthesized using established literature procedures, with some adaptations where necessary. Full details are given in the Supplementary material.

Almost 300 co-crystallization experiments were carried out in this study. Details of these experiments are also given in full in the Supplementary material. The choice of co-former was based on the potential to form strong supramolecular synthons. For example, phosphazenes containing pyridyl substituents were co-crystallized with molecules containing carboxylic acids or hydroxyl groups, in the hope that formation of a pyridyl...HO hydrogen bond would drive co-crystal formation. We also investigated co-formers that might form π–π interactions or halogen bonds. Finally, bulky or awkwardly-shaped molecules were also investigated as co-formers. For lists of co-crystal formers and solvates used, see Tables S1–S17 in the Supplementary material. Very few mechanochemical experiments were carried out, as this tended to result in degradation of the phosphazene ring, most likely forming phosphazene polymers. There were no issues with solubility of the phosphazenes used.

For the structures of **1**, **5**, and **10**–**12**, X-ray intensity data were collected on a Bruker-Nonius SMART Apex diffractometer equipped with a fine-focus sealed tube and a 0.5 mm Monocap collimator (monochromated Mo-Kα radiation, λ = 0.71073 Å). Data were captured with a CCD area-detector with the generator powered at 40 kV and 30 mA. The temperature of the crystal was controlled by constant stream of nitrogen gas produced by an Oxford Cryosystems Cryostat (700 Series Cryostream Plus). For the crystal structures of **6** and the co-crystal **7•TPA**, intensity data were collected on a Bruker Apex DUO CCD diffractometer with a multilayer monochromator. Mo-Kα radiation (λ = 0.71073 Å) was selected for the experiments. The temperature of the crystal was controlled using an Oxford Cryosystems Cryostream. Data reduction was done by means of a standard procedure using the Bruker software package SAINT[15] and the absorption corrections and the correction of other systematic errors were performed using SADABS.[16] The structures were solved by direct methods using SHELXS-97 and refined using SHELXL-97 and SHELXL-2014/7.[17] X-Seed[18] was used as the graphical interface for the SHELX program suite. Most hydrogen atoms were placed in calculated positions using riding models. Hydrogen atoms on nitrogen or oxygen atoms were located in the electron density difference map and allowed to refine.

Cambridge Structural Database[12] (CSD) searches were carried out using ConQuest[19] version 1.17 on version 5.36 with 3 updates (Nov. 2014, Feb. 2015, May 2015).

For powder X-ray diffraction analysis, samples were ground to a fine powder with a mortar and pestle and placed on a zero-background sample holder. Experiments were carried out on a PANalytical X'Pert PRO instrument in Bragg-Brentano geometry. Intensity data were collected using an X'Celerator detector and 2θ scans in the range of 5–50° were performed using Cu-Kα radiation (λ = 1.5418 Å).

Differential scanning calorimetry was carried out using a TA Instruments Q100 system under an N_2 gas purge, with a flow rate of 50.0 ml min^{-1}. The samples (ranging from 1.5 to 3 mg) were placed in aluminium pans that were non-hermetically sealed with vented aluminium lids. The heating rate for all experiments was 10 °C min^{-1}, and the cooling rate was 5 °C min^{-1}.

3. Results and Discussion

3.1. CSD Analysis

In order to give some idea of the frequency with which cyclotriphosphazenes form co-crystals or solvates, a Cambridge Structural Database search was carried out.[12] If the search is restricted to 'organic only' structures with 3D co-ordinates determined, 728 structures containing the cyclotriphosphazene moiety are identified. Of these, 26 are salts or zwitterions (identified by searching for any charged atom). These were removed (as salts are necessarily multi-component crystals). Of the remaining 702 structures, only 109, or 15.5 %, are multi-component crystals (>1 chemical residues). This is only slightly lower than the occurrence in the CSD as a whole, where 16.8 % (42 601/252 827) of non-ionic organic structures are multi-component crystals.

These results imply that co-crystal or solvate formation is no more or less likely to occur with cyclotriphosphazenes than with any other molecule.

3.2. Co-crystallization Experiments

3.2.1. *Co-crystallizations with* **1**

The choice of **1** as a potential co-crystal former was based on its paddlewheel conformation, which indicated that it may form inclusion compounds similar to those formed by TPP.[3,4,5,6] The NH-functional groups on **1** are also available as potential hydrogen bond donors. A number of co-crystallization experiments were carried out with **1** (Table S1). Only the crystallization from THF/hexane yielded crystals. These proved to be the known hydrate of **1** (CSD refcode COPVAE).[20] We have re-determined this structure at 173 K, and crystallographic data are given in Table 1. El Murr *et al.*[20] report the isolation of crystals of non-solvated **1** from the reaction mixture, but these crystals did not survive exposure to X-rays. However, the crystals grown from methanol that incorporated water into the structure did not disintegrate upon exposure to X-rays, suggesting that incorporation of water increases the stability of the crystal. It seemed likely that other hydrogen bonding solvents might also fulfil this role, and we therefore attempted crystallization from a number of hydrogen bonding solvents (donors and acceptors, see Table S1) in the hope of forming solvates. This was unsuccessful.

3.2.2. *Co-crystallization Experiments with* **2**, **3** *and* **4**

Numerous attempts to generate either solvates or co-crystals with **2**, **3** and **4** were made (see Tables S2, S4 and S6 in the Supplementary material). None of these experiments yielded multi-component crystals. In most cases either no crystals were obtained, or crystals of the starting materials were obtained.

In order to investigate whether additional energy might be required for co-crystal formation, mechanochemical experiments were carried out with **2**, **3** and **4**. These derivatives were

ground together with 4,4′-bipyridine, imidazole or benzimidazole (Tables S3, S5, S7). The products obtained on grinding both **2** and **3** with imidazole were sticky white substances, whereas all the other products were fine dry powders. The products of the grinding experiments were analysed by PXRD, which showed that all products consisted of physical mixtures of the reagents (see Supplementary material).

The product obtained by grinding **2** with benzimidazole was dissolved in THF. This yielded a pink precipitate with a powder pattern that differs from those of both **2** and benzimidazole. NMR analysis of this precipitate showed numerous signals in the ^{31}P spectrum that do not correspond with those normally observed for **2**. This could indicate that grinding the two components together resulted in substitution of the chloro groups on the cyclotriphosphazene ring, or that the cyclotriphosphazene ring has opened and polymerized. The material is clearly not a co-crystal of **2**.

3.2.3. *Crystal Structures of* **5** *and* **6**

Co-crystallization experiments were carried out with **5** in the expectation that the awkward shape of the molecule might cause inefficient packing in the solid state, resulting in inclusion of solvent molecules. Attempts were therefore made to crystallize **5** from a variety of solvents (Table S8). This yielded crystals of **5** in two cases (benzene and acetone). As the crystal structure of this material has not previously been reported, it is described here. Selected crystallographic data are given in Table 1.

Compound **5** crystallizes in the monoclinic space group $P2_1/n$. One of the benzaldehyde groups is disordered over two positions of approximately equal occupancy. The molecules form discrete dimers *via* an offset face-to-face interaction between benzaldehyde groups, and the dimers are arranged in chains with π-stacking interactions between the biphenyl groups (Fig. 1). There are no hydrogen bonds evident in the structure, confirming that the aldehyde moiety is not a particularly strong hydrogen bond acceptor. Despite this, **5** was co-crystallized with a wide range of hydrogen bond donors. These co-crystallization experiments are listed in Table S9 in the Supplementary material. The ratio of **5** to co-crystal former was 1:2 in most experiments in order to take into account the two aldehyde moieties that could potentially participate in hydrogen bonding interactions. None of these experiments yielded any co-crystals. Some crystallizations produced crystals of **5**, some produced crystals of the co-formers and some yielded no crystals at all.

Compound **6** was chosen for its potential to form supramolecular synthons through the nitrile functionality. It is sparingly soluble in most solvents, except for DMSO and DMF in which it readily dissolves. Several co-crystallization experiments were carried out with halogen-containing co-crystal formers (see Table S10); however, no co-crystals were obtained. Rod-shaped crystals of pure **6** were grown from a co-crystallization experiment with bromopentafluorobenzene in DMSO. Selected crystallographic details are given in Table 1.

Cyclophosphazene **6** crystallizes in *P*-1, with one molecule in the asymmetric unit. Two cyanophenyl moieties are approximately parallel to one another above the plane of the phosphazene ring, and another two below the plane of the ring are also approximately parallel to one another. The other two cyanophenyl moieties are twisted away from one another (Fig. 2a). The molecules stack on top of one another to give columns parallel to the crystallographic *c* axis (Fig. 2b). These columns pack alongside one another in a slightly offset fashion. There are no immediately apparent structure-directing intermolecular interactions in this structure.

3.2.4. *Co-crystallization Experiments with* **7** *and* **8**

Both **7** and **8** were chosen as possible co-crystal formers because of the potential for hydrogen bond formation with either the pyridyl or the hydroxyl functionality on the molecules. One of the few known cyclotriphosphazene co-crystals

Table 1 Selected crystal data for several cyclotriphosphazene derivatives.

	1	**5**	**6**	**7·TPA**	**9α**[21]	**10**	**11**	**12**
Ratio (phosphazene: other)	1:2	–	–	1:2.5	–	–	–	–
Chemical formula	$C_9H_{28}N_9O_2P_3$	$C_{38}H_{26}N_3O_8P_3$	$C_{42}H_{24}N_9O_6P_3$	$C_{50}H_{39}N_9O_{16}P_3$	$C_{36}H_{24}F_6N_3O_6P_3$	$C_{36}H_{24}Cl_6N_3O_6P_3$	$C_{36}H_{24}Br_6N_3O_6P_3$	$C_{36}H_{24}I_6N_3O_6P_3$
Formula weight/ g mol^{-1}	387.31	745.53	843.61	1114.81	801.49	900.19	1166.95	1448.89
Crystal system	Triclinic	Monoclinic	Triclinic	Triclinic	Monoclinic	Monoclinic	Orthorhombic	Monoclinic
Space group	*P*-1	$P2_1/n$	*P*-1	*P*-1	$P2_1/n$	$P2_1/n$	*Pnma*	$P2_1/c$
Z	4	4	2	2	4	4	4	4
a/Å	11.342(6)	10.897(2)	12.004(1)	7.943(4)	20.323(2)	17.642(1)	31.460(3)	13.472(1)
b/Å	11.374(6)	15.131(2)	12.315(1)	13.238(6)	8.051(8)	7.503(5)	13.367(1)	9.396(9)
c/Å	14.515(8)	20.907(3)	13.970(1)	23.627(1)	21.694(2)	27.914(2)	9.122(7)	32.635(3)
α/°	76.12(1)	90	80.628(2)	76.504(1)	90	90	90	90
β/°	76.43(1)	103.440(2)	80.015(2)	80.357(1)	103.831(1)	91.899(1)	90	96.230(1)
γ/°	86.69(1)	90	71.023(1)	85.375(1)	90	90	90	90
Calculated density/g cm^{-3}	1.456	1.477	1.466	1.556	1.545	1.619	2.021	2.343
Cell volume/Å^3	1767.2(2)	3352.8(9)	1910.8(3)	2379.5(2)	3446.6(6)	3692.7(4)	3836.1(5)	4106.7(7)
Temperature/K	173(2)	100(2)	100(2)	100(2)	100(2)	103(2)	173(2)	100(2)
μ/mm^{-1}	0.360	0.239	0.220	0.212	0.258	0.648	6.456	4.704
Independent reflections	7360	3978	10363	11875	8117	6518	3514	7268
R_{int}	0.0153	0.0519	0.0454	0.0325	0.0290	0.0239	0.0550	0.0235
R_1 [$I > 2(I)$]	0.0366	0.0601	0.0402	0.0374	0.0344	0.0281	0.0299	0.0309

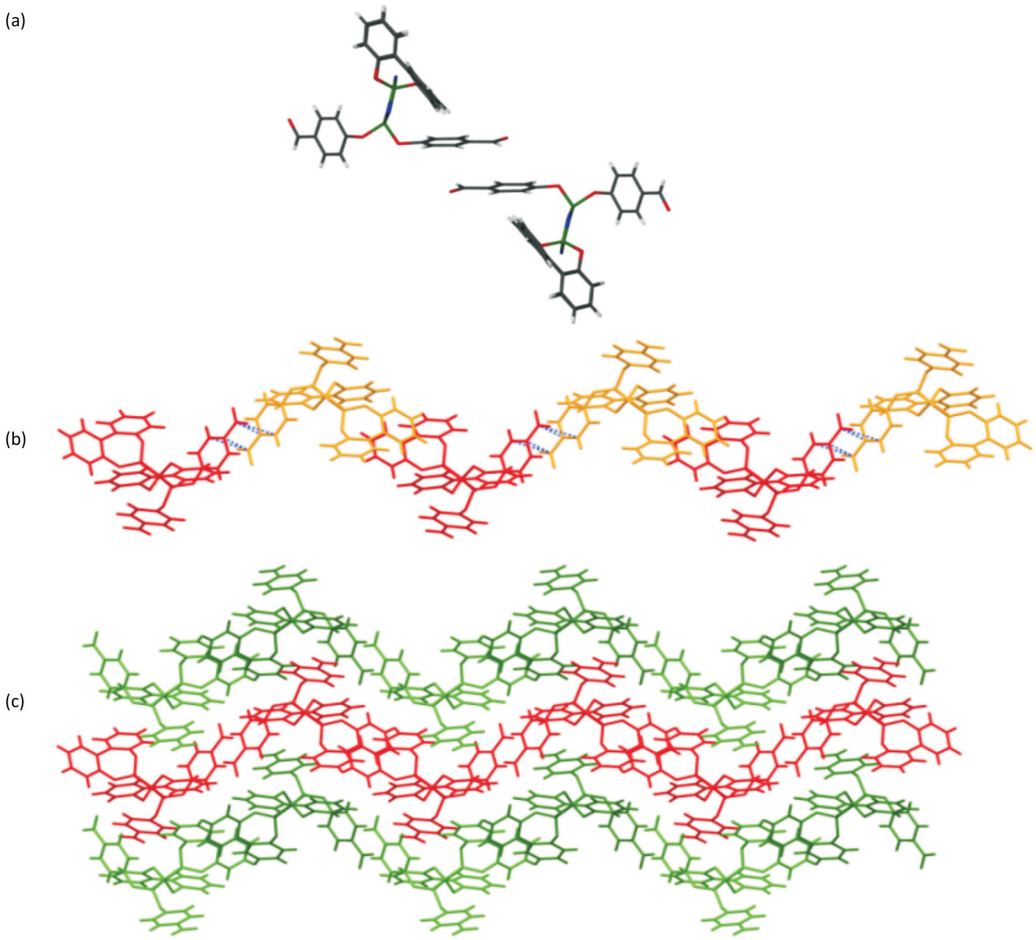

Figure 1 Packing in **5**. (**a**) The benzaldehyde moieties form discrete dimers *via* an offset face-to-face interaction. The structure can be viewed as though the dimers form chains as shown in (**b**), indicated by the blue dotted lines. This is viewed down the crystallographic *a* axis. The chains then close-pack as shown in (**c**), with close contacts between the biphenyl-2,2′-diol groups.

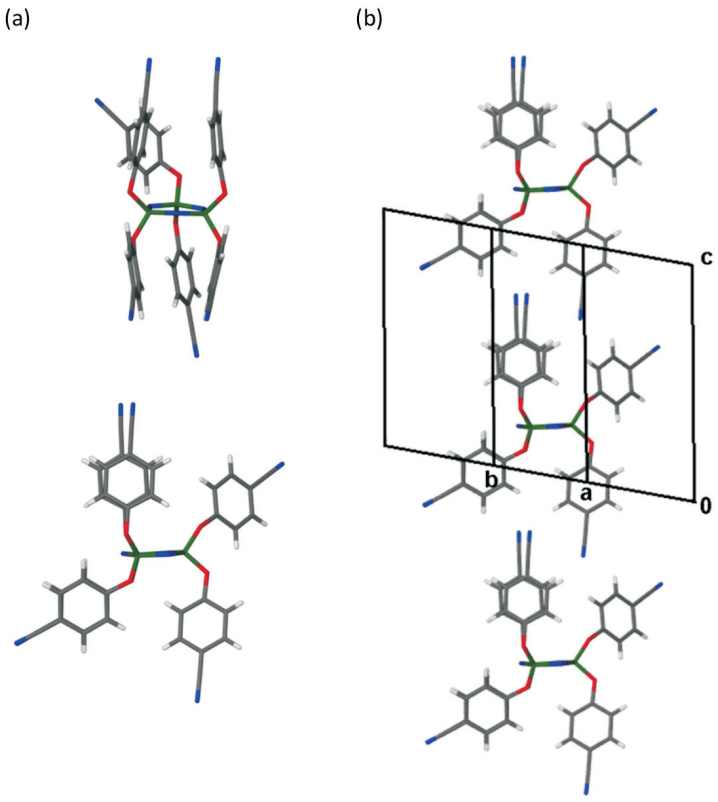

Figure 2 Packing in **6**. (**a**) Orientation of the cyanophenyl moieties in **6**. (**b**) Columns of molecules formed in **6**.

not based on TPP contains hexakis(4-pyridylcarbinoxy)cyclotriphosphazene, which is closely related to **7** (although the 3-D coordinates for this co-crystal structure are not in the CSD). Compound **7** therefore seemed a particularly promising candidate for co-crystal formation.

Numerous co-crystallization experiments were carried out with both **7** and **8** (Tables S11 and S12 in the Supplementary material). No co-crystals containing **8** were isolated. However, **7** was found to form a co-crystal with terephthalic acid, **7•TPA**. Crystallographic data are given in Table 1.

The crystals of **7•TPA** were grown from a 1:2 ratio of **7**:terephthalic acid in a layered solution of chloroform and DMF. Crystals of **7** were dissolved in chloroform and the terephthalic acid in DMF. Care had to be taken to add the two solutions together slowly as terephthalic acid is insoluble in chloroform and precipitates out of solution when chloroform is added to DMF. The co-crystal, which contains 2.5 terephthalic acid molecules for every molecule of **7**, crystallizes in *P*-1. No charge transfer has taken place, *i.e.* both carboxylic acid groups of each terephthalic acid molecule are protonated, and these form hydrogen bonds with the pyridyl groups on the cyclotriphosphazene. Five of the six pyridyl groups on the cyclotriphosphazene ring are involved in hydrogen bonding with a terephthalic acid molecule through a COOH···N interaction with the hydroxyl group of the carboxylic acid. This results in an infinite hydrogen-bonded chain (Fig. 3a). The terephthalic acid molecules shown in orange in Fig. 3b link neighbouring chains through hydrogen bonding to a pyridyl group in the next chain.

It seems likely that the hydrogen bonds between **7** and terephthalic acid are strong interactions, driving the formation of a co-crystal. It is surprising, however, that no other co-crystals with di-acids were isolated with this derivative despite this seemingly strong interaction. This could indicate that the correct shape match is very important in forming co-crystals with cyclotriphosphazenes.

3.2.5. *Co-crystallization Experiments with* **9–12**

The hexakis(4-halophenoxy)cyclotriphosphazene derivatives **9–12** were synthesized in order to investigate whether co-crystals could be formed using supramolecular synthons involving halogens. These derivatives were co-crystallized with a range of small molecules, including molecules containing halogens, nitriles and nitrogen-containing heterocycles such as pyridine. The solvent systems that were used include acetonitrile, acetonitrile/DCM, DCM, THF, THF/methanol, chloroform, chloroform/acetone and DMSO, as well as combinations of these solvents (Tables S13–16). In each case the cyclotriphosphazene derivative crystallized as the pure material, rather than co-crystallizing with other small molecules.

The crystal structures of **9–12** were originally determined at room temperature.[20] Our previous observation of polymorphism in **9**[21] led us to redetermine the structures at 100 K, and the data are included here for completeness (see Table 1). On analysis of the crystal structures of these derivatives, it is apparent that hexakis(4-fluorophenoxy)cyclotriphosphazene (**9**) and hexakis(4-chlorophenoxy)cyclotriphosphazene (**10**) are isostructural, and that hexakis(4-bromophenoxy)cyclotriphosphazene (**11**) and hexakis(4-iodophenoxy)cyclotriphosphazene (**12**) are isostructural. The only differences between the structures are slight changes in the twist of the phenoxy rings between derivatives. DSC was also carried out on **9–12**, but only **9** showed any evidence of polymorphism in the temperature range investigated.

The isostructurality between **9** and **10**, as well as **11** and **12**, implied that combinations of these molecules may lead to co-crystal formation. Unfortunately, co-crystals of **9** with **10**, or **11** with **12**, could not be grown from solution. The growth of co-crystals by melting the isostructural compounds together was then investigated (Table S17). Crystals of **9** and **10** were ground together in a 1:1 ratio, melted and DSC analysis was performed on the product. DSC analysis showed that the melting point of the product (referred to as **9**/**10**) is at 122.9 °C, which is lower than the melting point of both **9** (129 °C) and **10** (152 °C). The same procedure was followed for **11** and **12**, and again there is only one melting point at 173.1 °C. The melting point of **11** is 176.8 °C and that of **12** is 187.6 °C. This is, however, not conclusive evidence that a co-crystal has formed.

PXRD analysis was carried out on the melt products **9**/**10** and **11**/**12**. The results are shown in Fig. 4. PXRD analysis is unfortunately also not conclusive. In both cases, the powder patterns of

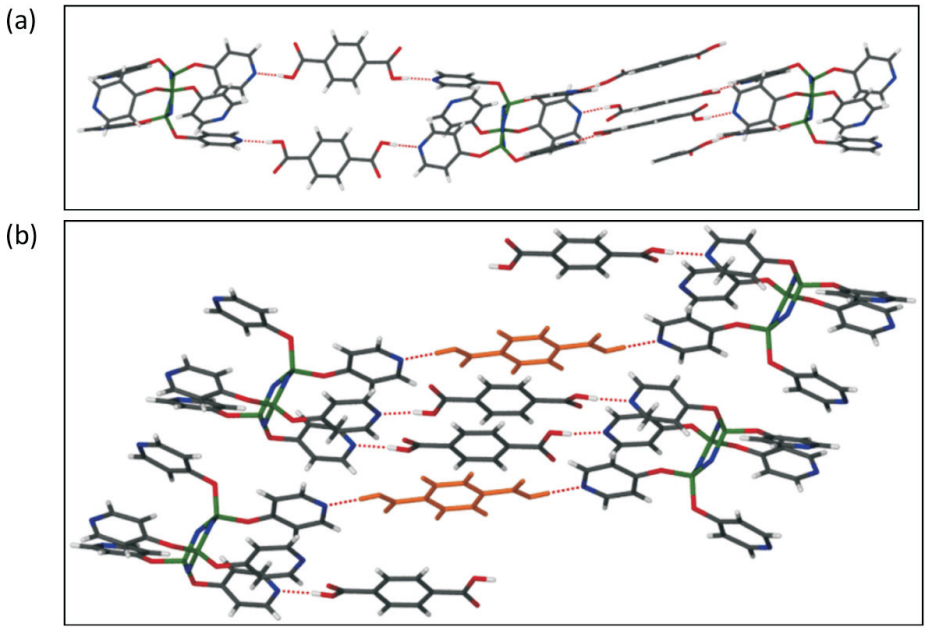

Figure 3 (**a**) The infinite hydrogen-bonded chain formed in **7•TPA**. (**b**) The hydrogen-bonded chains are linked *via* a terephthalic acid molecule, shown here in orange, that hydrogen bonds to the pyridyloxy group of a neighbouring cyclotriphosphazene molecule.

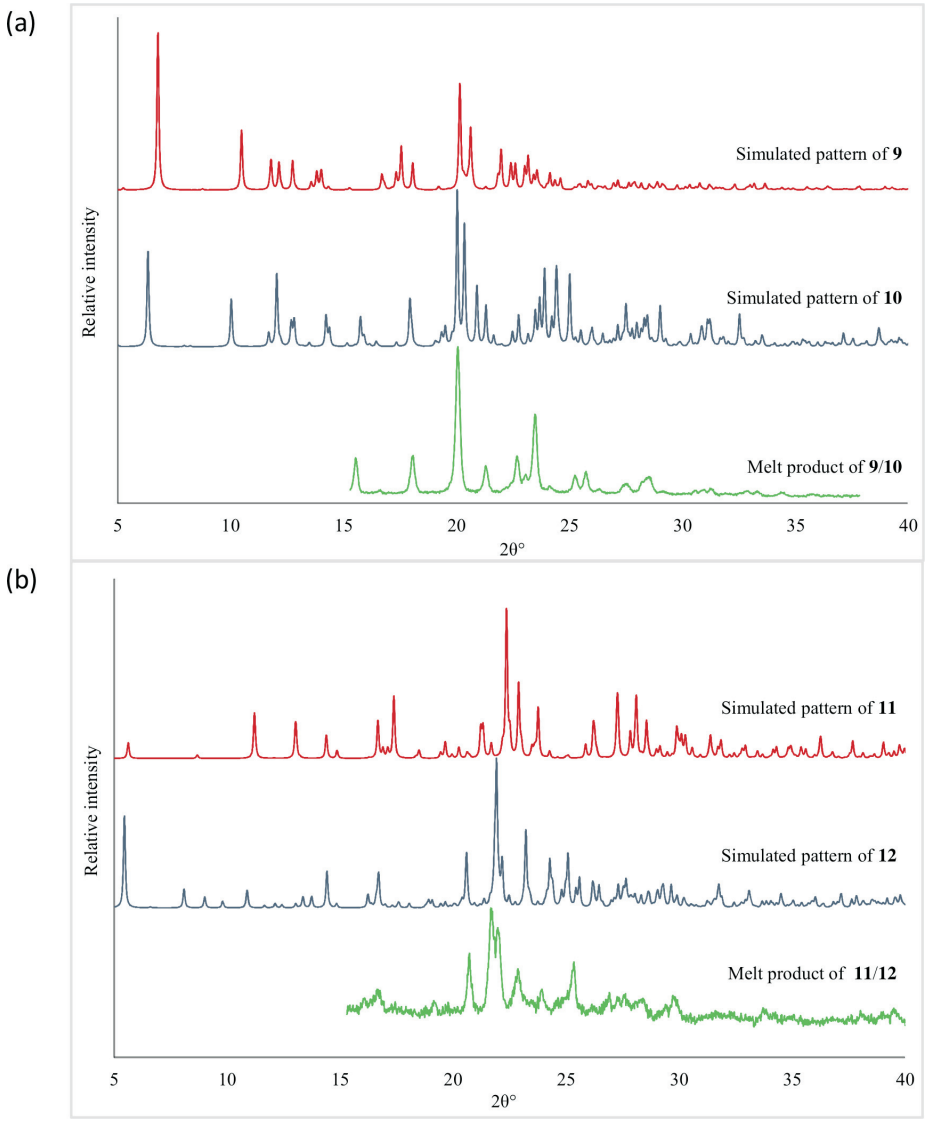

Figure 4 (**a**) PXRD analysis of the melt product **9/10**. The pattern of **9/10** corresponds with the patterns of **9** and **10** to a large extent, but the results are not conclusive. (**b**) PXRD analysis of the melt product of **11/12**.

the melt products largely correspond to the simulated patterns of the halophenoxy derivatives. There are minor differences between the patterns, but it is difficult to determine whether a novel co-crystal has in fact formed. It is likely that any co-crystals formed would be isostructural to the co-crystal formers, and hence have similar powder patterns. The melt products could also be solid solutions, as opposed to stoichiometric co-crystals. We are thus unable to state conclusively whether these derivatives form co-crystals from the melt.

3.3. Lack of Co-crystal Formation

During this investigation, a total of nearly 300 co-crystallization experiments were carried out using 12 different cyclophosphazene derivatives and a number of crystallization techniques, and only one co-crystal was obtained. Largely, the crystals that were obtained were of the pure cyclotriphosphazene derivative, with only one derivative (**1**) crystallizing as a hydrate and no derivatives crystallizing as solvates. This is a remarkably low success rate – the CSD study indicates that around 15 % of cyclotriphosphazene-containing structures are multi-component crystals. Why then was our success rate so low?

The most obvious explanation is that the supramolecular synthons employed were simply not strong enough to promote co-crystallization, *i.e.* the heteromeric interactions were not as strong as the homomeric interactions. This may well have been the case for many of the combinations that were attempted, although in a number of the molecules selected there are no obvious strong intermolecular interactions in the crystals of the pure material. However, this does not explain why a co-crystal could be formed between **7** and terephthalic acid, but not between **7** and any other carboxylic acids, despite numerous attempts.

Inspection of the pK_a values of the acids used (Table 2)[22] indicates that this is not simply a case of acid strength (and by extension hydrogen bond strength). There are clearly other factors involved.

It does appear that the size and shape of the co-crystallization agent plays a role. A study conducted by Anderson *et al.*[23] found that molecules that crystallize with $Z' > 1$ are generally small, awkwardly shaped molecules. They are also more conformationally restricted, which might explain why the cyclotriphosphazenes seldom co-crystallize with smaller molecules: cyclotriphosphazenes are much larger molecules with substituents that are more conformationally flexible. It has also been suggested that polymorphic molecules make better

Table 2 pK_a values of various carboxylic acids.

Acid	pK_a[21]
Adipic acid	4.41, 5.41
Citric acid	3.13, 4.76, 6.40
Fumaric acid	3.02, 4.38
Isophthalic acid	3.70, 4.60
Maleic acid	1.92, 6.23
Malic acid	3.40, 5.11
Pamoic acid	2.51, 3.10
Succinic acid	4.21, 5.64
Tartaric acid (DL)	3.03, 4.37
Terephthalic acid	3.54, 4.34
Trimesic acid	3.12, 3.89, 4.70

co-crystal formers.[24] We do not observe this: compound **9** is highly polymorphic, with four known polymorphs, yet no co-crystals of this molecule were isolated. In this case, the conformational flexibility of the molecule results in it crystallizing in a number of ways – the molecule can solve the problem of close-packing without the need for a co-former. In order to improve the probability of obtaining co-crystals or solvates with cyclotriphosphazenes, the substituents on the P-N ring should be conformationally restricted (no flexible O linkage). Functional groups on the substituents should be strong hydrogen bond donors or acceptors, or strong halogen bond acceptors (such as iodine where the acceptor strength has been increased by fluorination).

This study aimed to isolate co-crystals from solution, in the manner one might carry out a co-crystal screen for a pharmaceutical molecule. The difficulty encountered in obtaining co-crystals was not at all anticipated. It is possible that with further detailed investigation, the particular conditions to form co-crystals of these molecules could be identified. Several avenues were pursued to try and explain the low success rate, including analysis of what preferred co-crystal formers might be. None of these offered any insight – in fact, all analysis indicated that we should be able to form other co-crystals with **7**. It is particularly interesting that no further co-crystals between **7** and carboxylic acids were obtained. No obvious explanation for this can be identified.

4. Conclusions

An extensive investigation of co-crystal formation with 12 cyclotriphosphazene derivatives has been carried out. Around 300 co-crystallization experiments were carried out, but only one co-crystal was obtained. These results clearly indicate that many cyclotriphosphazenes have a very low tendency to form co-crystals. There is no clear explanation for this, but it serves as a caution: the formation of co-crystals is not necessarily trivial, and certainly more investigation is needed to shed light on why this is the case.

Acknowledgements

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Supplementary Material

Details of co-crystallization experiments, PXRD, NMR, DSC and synthetic details are available as supplementary information. X-ray crystallographic data are available in cif format. CCDC 1055282-1055288 contain the crystallographic data for this manuscript. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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* This material is based upon work supported financially by the National Research Foundation of South Africa. Any opinion, findings and conclusions or recommendations expressed in this material are those of the authors and therefore the NRF does not accept any liability in regard thereto.

interactions in the crystal structure. There are however no 3D-coordinates for this structure in the Cambridge Structural Database.

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Lack of co-crystal formation with cyclotriphosphazenes: a cautionary tale

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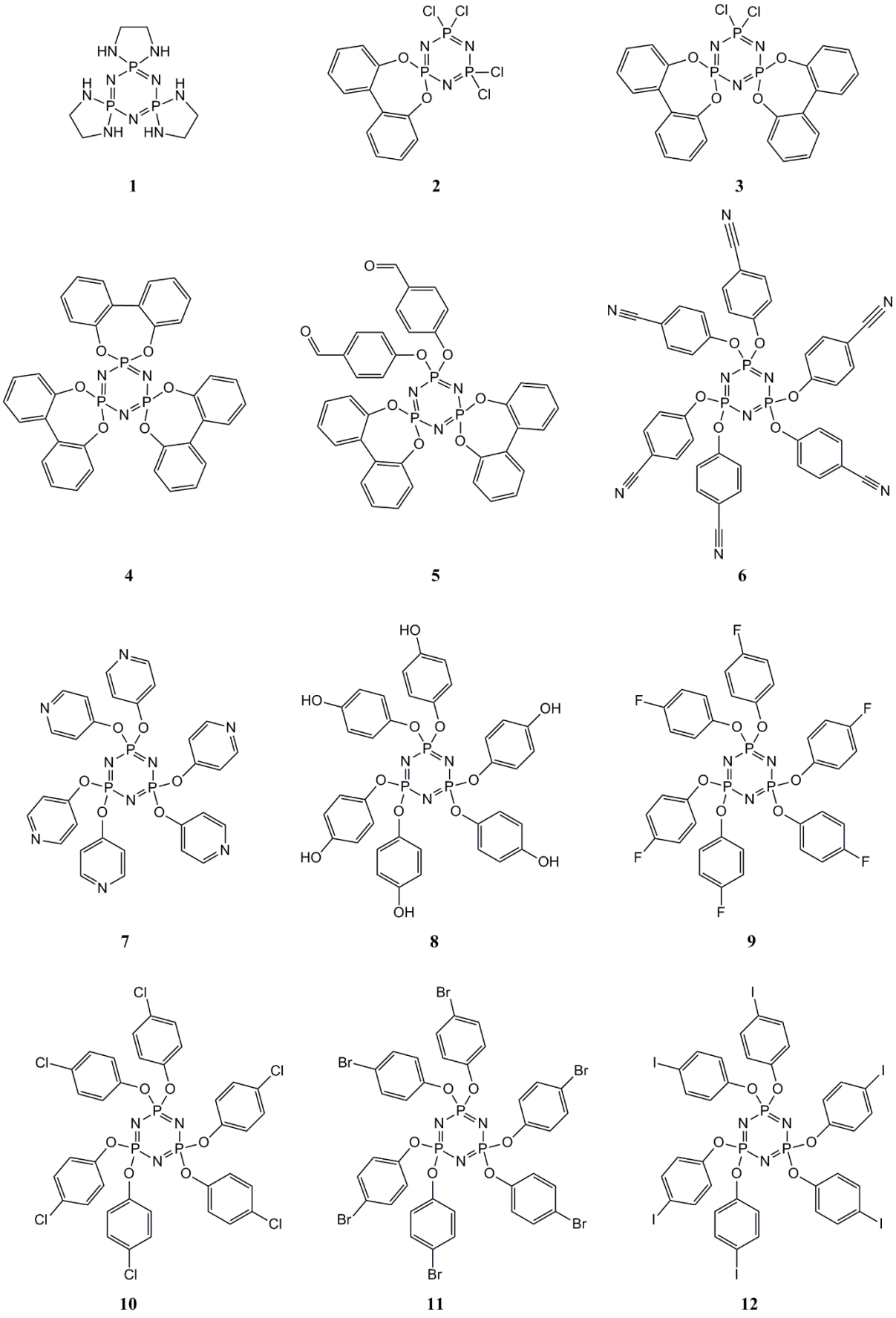
Supporting Information



Scheme S1 The cyclotriphosphazenes investigated in this work.

Co-crystallisation experiments

The components of each crystallisation experiment (see Tables S1, S2, S4, S6, S8-14) were dissolved in the appropriate solvent with gentle heat and stirring. In cases where there were still undissolved particles, the solution was filtered through a non-sterile 33 mm Millex-HV syringe filter unit into a glass vial. All solutions were left to stand at room temperature and crystals were formed either *via* slow evaporation of the solvent, vapour diffusion of one solvent into another or solutions were layered with a second solvent to induce crystal formation at the interface of the two solutions.

Table S1 Co-crystallisation experiments carried out with **1**. All crystallisations were carried out *via* slow evaporation. Crystals obtained were that of the known hydrate of **1** (CSD-COPVAE) or no product was obtained.

Co-former	**Quantity (1; co-former) /mg**	**Mole ratio (1:co-former)**	**Solvent system**	**Product**
isophthalic acid	29; 14	1:1	methanol	none
terephthalic acid	15; 15	1:2	methanol	terephthalic acid
trimesic acid	29; 20	1:1	methanol	none
succinic acid	14; 15	1:3	methanol	none
maleic acid	13; 13	1:3	methanol/THF	none
tartaric acid	13; 12	1:3	methanol	none
2,6-naphthalene dicarboxylic acid	29:18	1:1	methanol	2,6-naphthalene dicarboxylic acid
solvent	-	-	THF	none
solvent	-	-	hexane/THF	known COPVAE
solvent	-	-	DCM	none
solvent	-	-	DMSO	none
solvent	-	-	acetonitrile	known COPVAE
solvent	-	-	methanol	none
solvent	-	-	ethanol	none
solvent	-	-	DMF	none
solvent	-	-	NMP	none
solvent	-	-	chloroform	none

Table S2 Co-crystallisation experiments carried out with **2**. All crystallisations were carried out *via* slow evaporation. In some cases crystals of the starting materials were obtained, otherwise no crystals were obtained.

Co-former	Quantity (2; co-former) /mg	Mole ratio (2:co-former)	Solvent system	Product
DCM	50	As solvent	-	none
benzene	45	As solvent	-	none
toluene	46	As solvent	-	none
chloroform	54	As solvent	-	none
acetonitrile	49	As solvent	-	none
pyridine	48	As solvent	-	none
1,4-dioxane	55	As solvent	-	none
NMP	51	As solvent	-	none
THF	74	As solvent	-	none
DMF	68	As solvent	-	none
isophthalic acid	53; 41	1:2	DCM/THF	none
imidazole	55; 25	1:3	DCM/THF	none
benzimidazole	59; 33	1:3	DCM/THF	benzimidazole hydrate
4,4'-bipyridine	52; 35	1:2	DCM/THF	none
benzonitrile	54	As solvent	-	none
3,4-lutidine	62; 35	1:3	DCM	none

Table S3 Mechanochemical experiments carried out with **2**. Samples were ground by hand in a mortar and pestle for approximately 5 minutes, yielding homogenous powders.

Co-former	Quantity (2; co-former) /mg	Mole ratio (2: co-former)
4,4'-bipyridine	28; 32	1:2
imidazole	56; 24	1:2
benzimidazole	51; 28	1:2
4,4'-bipyridine	62; 21	1:1
imidazole	61; 10	1:1
benzimidazole	64; 15	1:1
piperazine	61; 12	1:1
4,4'-trimethylene dipyridine	65; 30	1:1

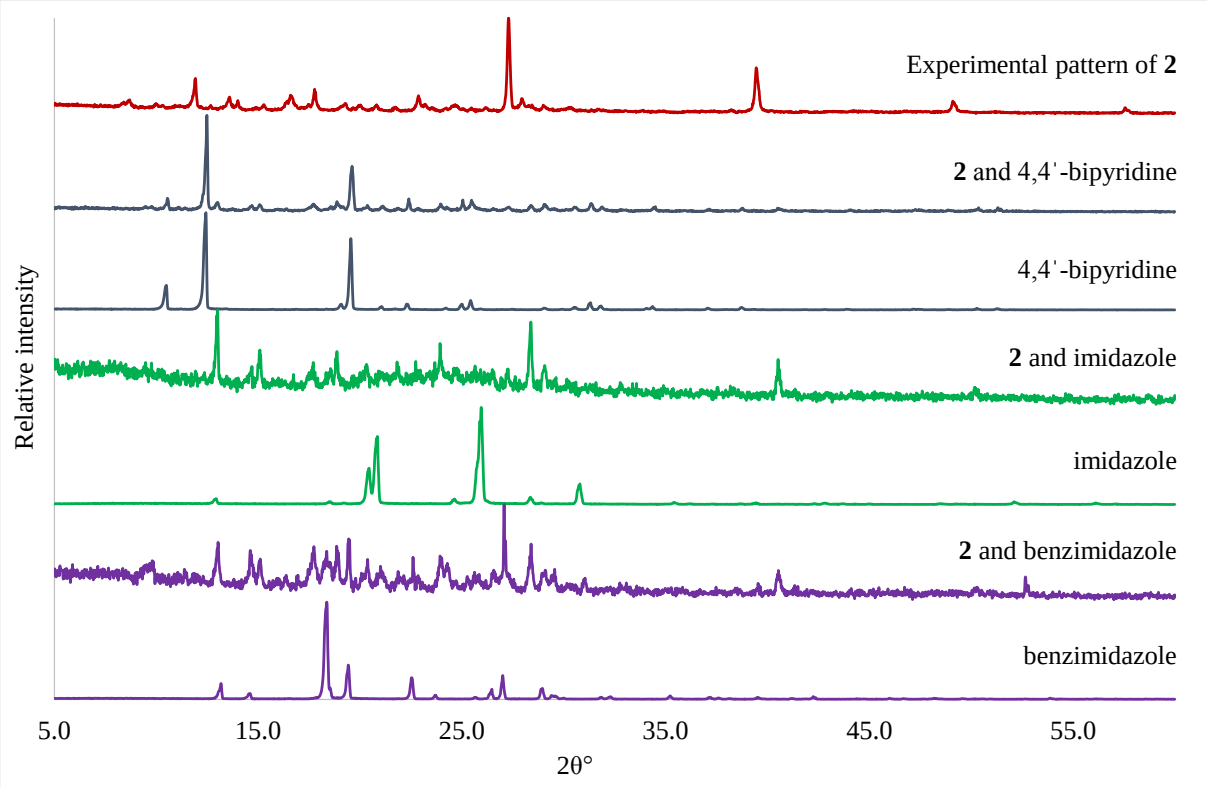


Figure S1 PXRD results of the grinding experiments with **2**. The powder patterns of the products either correspond to that of **2** or the co-crystal former.

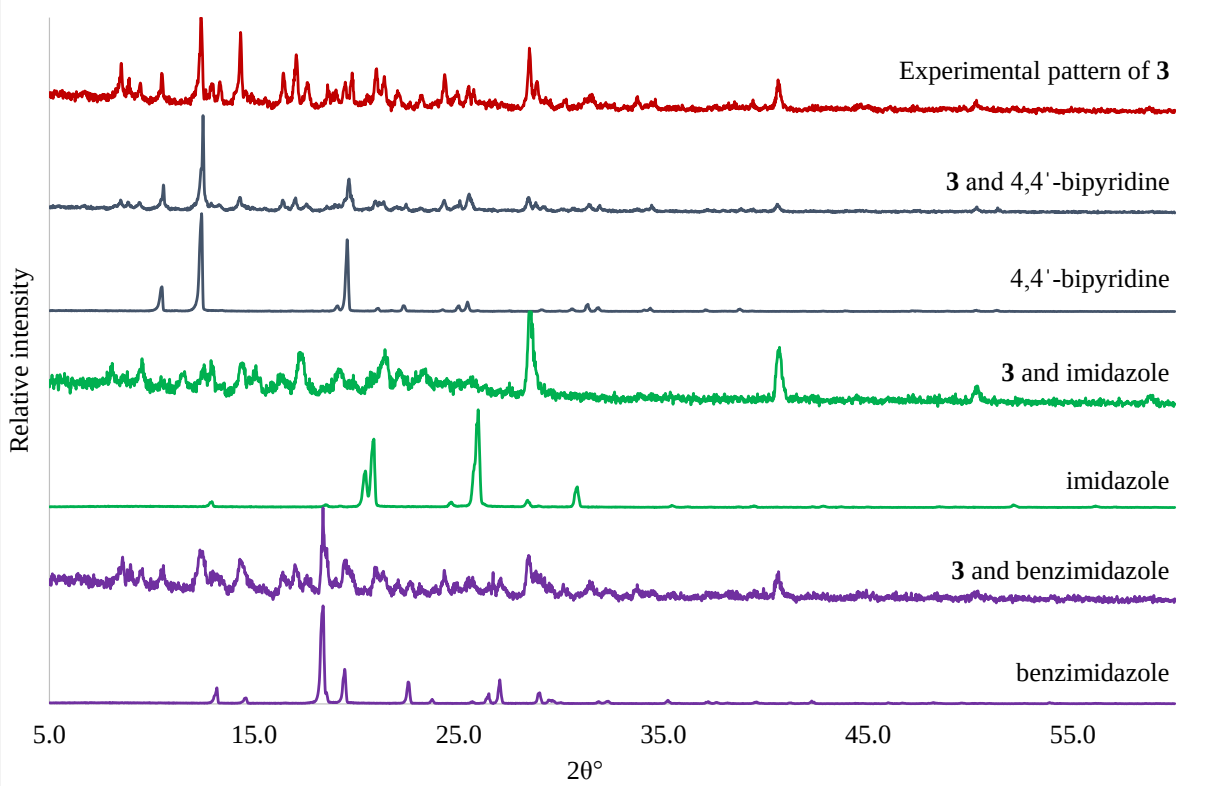


Figure S2 The PXRD results of the mechanochemical experiments between **3** and 4,4'-bipyridine, imidazole and benzimidazole. In most cases there appears to be an agreement between the patterns of the product and 4,4'-bipyridine, imidazole and benzimidazole.

Table S4 Co-crystallisation experiments carried out with **3**. All crystallisations were carried out *via* slow evaporation. In most cases no crystals were obtained, and in a few cases crystals of the starting materials were obtained.

Co-former	Quantity (3; co-former) /mg	Mole ratio (3: co-crystal former)	Solvent system	Product
4,4'-bipyridine	108; 111	1:3	DCM	none
imidazole	107; 65	1:3	DCM	none
benzimidazole	103; 83	1:3	DCM	benzimidazole hydrate
m-xylene	100	excess	*m*-xylene	none
benzene	59	As solvent	-	none
toluene	60	As solvent	-	Known **3**
DCM	60	As solvent	-	none
chloroform	57	As solvent	-	none
acetonitrile	53	As solvent	-	none
pyridine	52	As solvent	-	none
1,4-dioxane	57	As solvent	-	none
NMP	63	As solvent	-	none
THF	62	As solvent	-	none
DMF	67	As solvent	-	none
isophthalic acid	62; 35	1:2	DCM/THF	none
imidazole	69; 15	1:2	DCM/THF	none
benzimidazole	63; 31	1:2	DCM/THF	none
4,4'-bipyridine	63; 33	1:2	DCM/THF	none

Table S5 Mechanochemical experiments carried out with **3**. Samples were ground by hand in a mortar and pestle for approximately 5 minutes, yielding homogenous powders.

Co-former	Quantity (3; co-former) /mg	Mole ratio (3: co-former)
4,4'-bipyridine	62; 33	1:2
imidazole	61; 14	1:2
benzimidazole	60; 13	1:2

Table S6 Summary of crystallisation experiments with **4** in a range of solvents and with a series of potential co-crystal formers. All crystallisations were carried out *via* slow evaporation. Only one crystal of **4** was obtained.

Co-former	**Quantity (4; co-former) /mg**	**Mole ratio (4: co-former)**	**Solvent system**	**Product**
benzene	58	-	-	none
toluene	61	-	-	none
DCM	60	-	-	known **4**
chloroform	58	-	-	none
pyridine	60	Excess	-	none
acetonitrile	62	-	-	none
dioxane	60	-	-	none
NMP	59	-	-	none
THF	61	-	-	none
DMF	60	-	-	none
m-xylene	60	-	-	none
isophthalic acid	60; 51	1:3	THF	none
imidazole	61; 21	1:3	THF	none
benzimidazole	63; 36	1:3	THF	none
4,4'-bipyridine	62; 48	1:3	THF	none

Table S7 Mechanochemical experiments carried out with **4**. Samples were ground by hand in a mortar and pestle for approximately 5 minutes, yielding homogenous powders.

Co-former	**Quantity (4; co-former) /mg**	**Mole ratio (4: co-former)**
4,4'-bipyridine	61; 20	1:1
imidazole	61; 9	1:1
benzimidazole	64; 14	1:1
piperazine	63; 9	1:1
4,4'-trimethylene dipyridine	63; 28	1:1

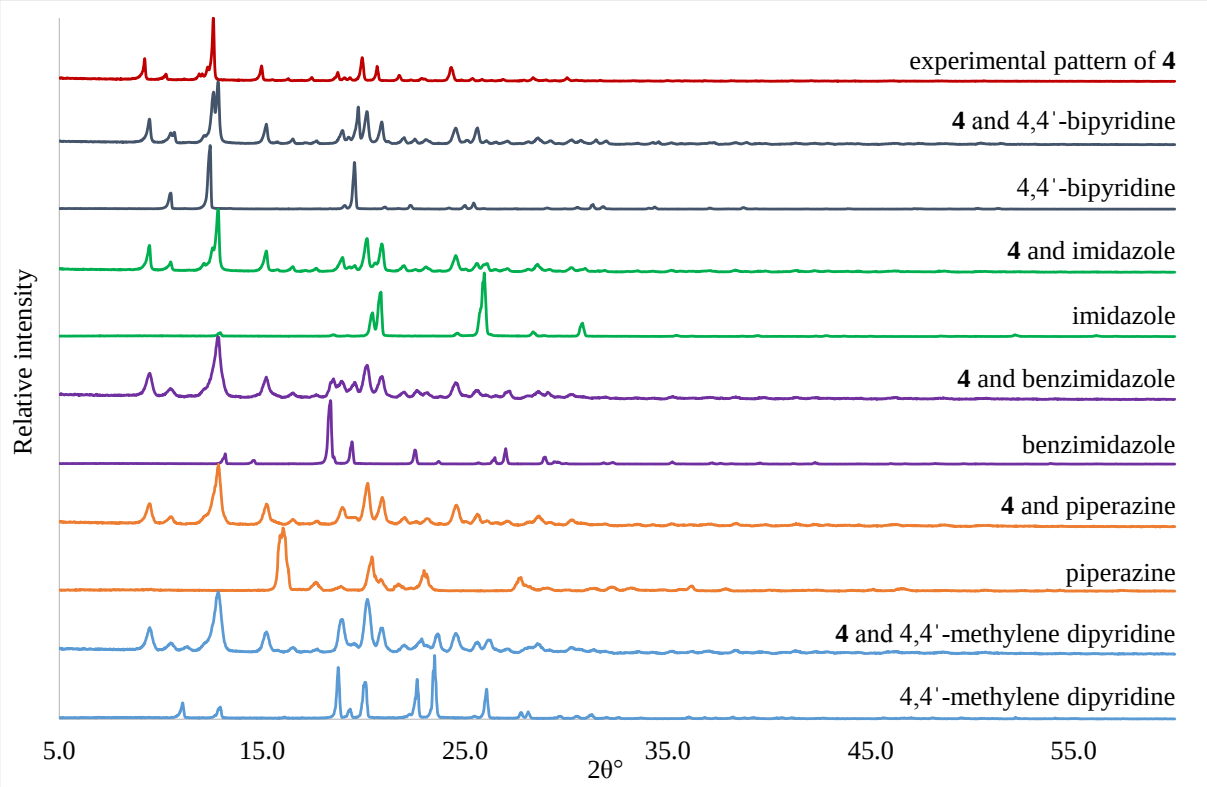


Figure S3 The PXRD results of mechanochemical experiments with **4**. In all cases the product of the grinding experiment corresponds to the powder pattern of **4**, indicating that no co-crystals were formed.

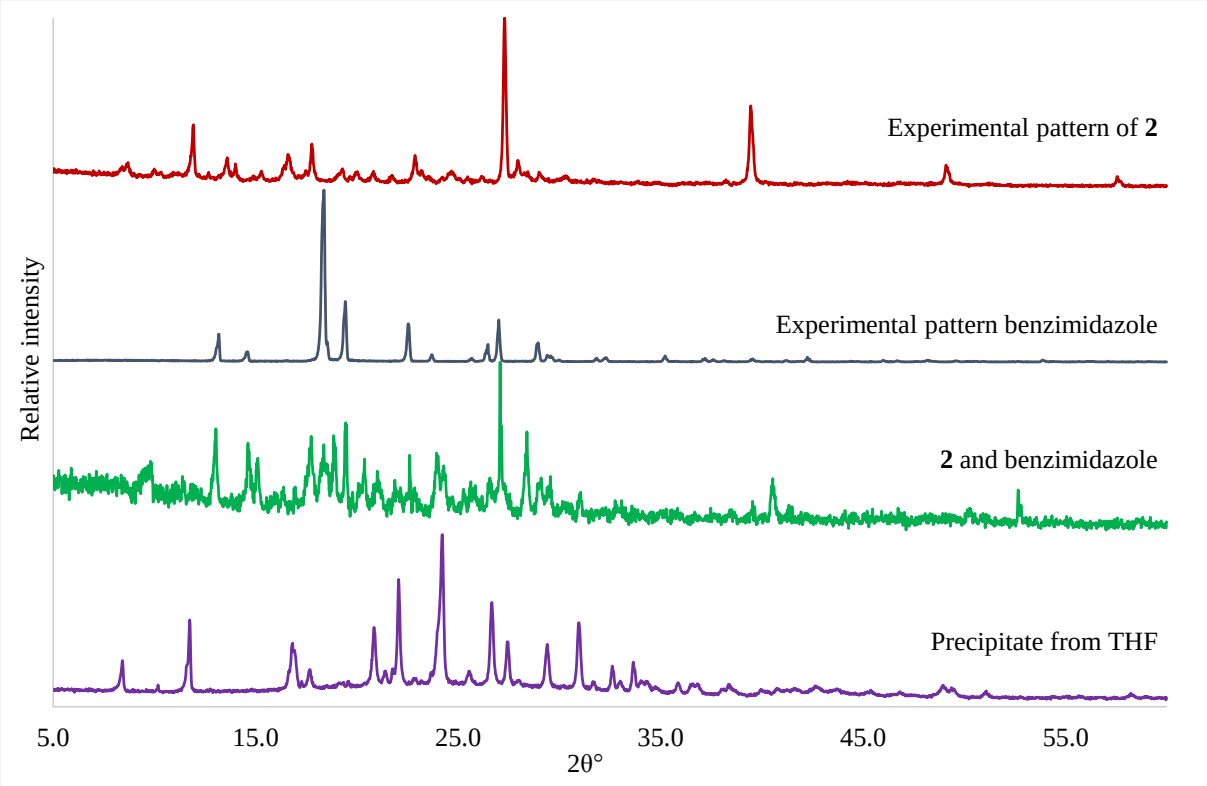


Figure S4 The PXRD results of the precipitate formed when the product of mechanochemical synthesis between **2** and benzimidazole is dissolved in THF.

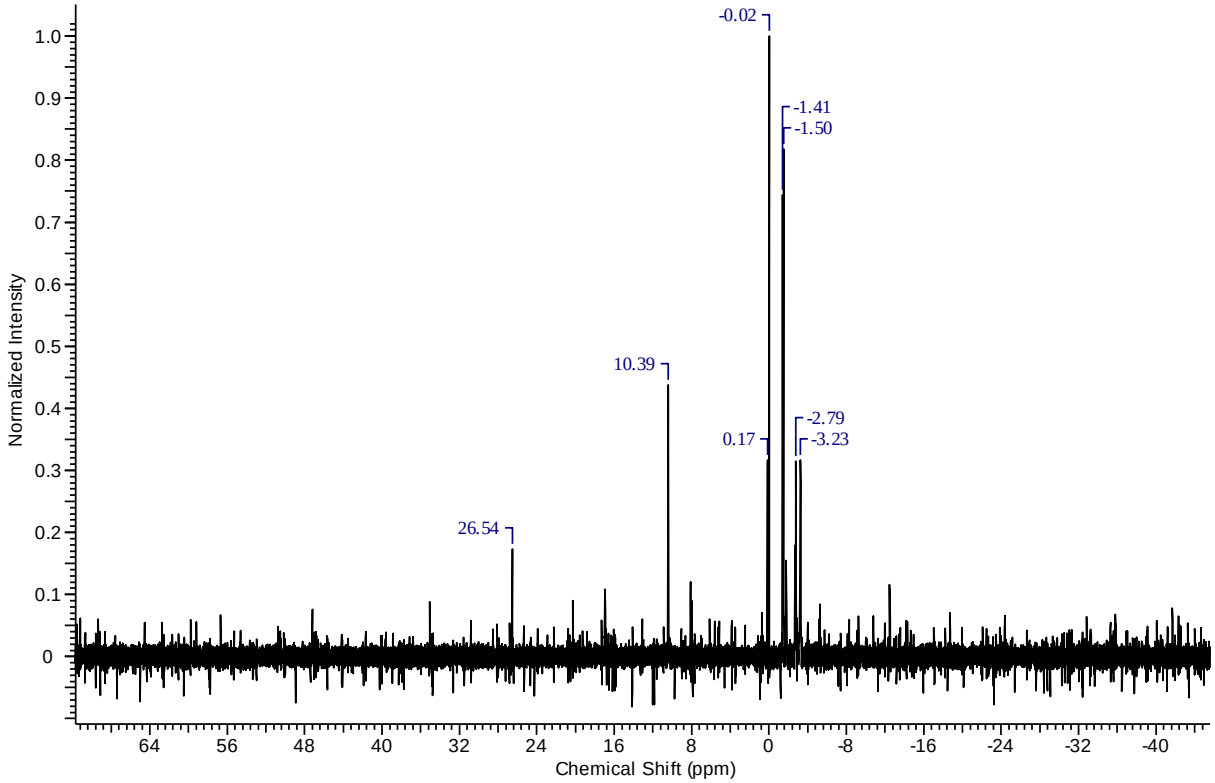


Figure S5 The ^{31}P NMR spectrum of the precipitate formed when the product of mechanochemical synthesis between **2** and benzimidazole is dissolved in THF. Multiple peaks for phosphorous indicates that ring cleavage could have occurred.

Table S8 Summary of crystallisation experiments with **5** from a range of solvents. Approximately 60 mg of **5** was used in each crystallisation.

Solvent system	**Co-crystal former**	**Crystallisation technique**	**Result**
benzene	none	slow evaporation	crystals of **5**
toluene	none	slow evaporation	no crystalline product
methanol	none	slow evaporation	no crystalline product
NMP	none	slow evaporation	no crystalline product
DMSO	none	slow evaporation	no crystalline product
chloroform	none	slow evaporation	no crystalline product
acetone	none	slow evaporation	crystals of **5**

Table S9 Co-crystallisation experiments carried out with **5**.

Co-former	Quantity (5; co-former) /mg	Mole ratio (5: co-former)	Solvent system	Crystallisation technique	Product
pamoic acid	44; 21	1:1	THF	slow evaporation	none
piperazine	40; 6	1:1	THF	slow evaporation	none
2,6-diaminopyridine	41; 7	1:1	THF	slow evaporation,	none
trimesic acid	46; 12	1:1	THF/hexane	layering	trimesic acid and hexane
isophthalic acid	41; 10	1:1	THF/hexane	layering	none
benzonitrile	42; excess	-	THF	slow evaporation	none
2,6-diaminopyridine	40; 12	1:2	THF/diethyl ether	vapour diffusion	none
1,2-diaminoethane	42; 20	1:6	THF/diethyl ether	vapour diffusion	none
1,3-diaminopropane	43; 21	1:6	THF/diethyl ether	vapour diffusion	none
1,4-diaminobutane	42; 15	1:3	THF/diethyl ether	vapour diffusion	none none
1,5-diaminopentane	42; 18	1:3	THF/diethyl ether	vapour diffusion	none
1,6-diaminohexane	41; 15	1:3	THF/diethyl ether	vapour diffusion	none
piperazine	40; 12	1:2	THF/diethyl ether	vapour diffusion	none
p-aminobenzoic acid	40; 15	1:2	DCM/diethyl ether	vapour diffusion	none
p-aminobenzoic acid	40; 17	1:2	DMF/diethyl ether	vapour diffusion	none
2-aminoterephthalic acid	41; 21	1:2	THF/diethyl ether	vapour diffusion	crystals of **5**
2-aminoterephthalic acid	43; 21	1:2	DMF/diethyl ether	vapour diffusion	none
2,6-dipicolinic acid	42; 21	1:2	THF/DCM	vapour diffusion	none
2,6-dipicolinic acid	43; 19	1:2	DMF/ether	vapour diffusion	crystals of **5**
3,5-dinitrobenzoic acid	40; 30	1:2	THF/diethyl ether	vapour diffusion	3,5-dinitrobenzoic acid
3,5-dinitrobenzoic acid	43; 25	1:2	DMF/diethyl ether	vapour diffusion	none
1,6-dihydroxynaphthalene	42; 19	1:2	THF/diethyl ether	vapour diffusion	crystals of **5**
1,6-dihydroxynaphthalene	45; 19	1:2	DMF/diethyl ether	vapour diffusion	crystals of **5**
o-phenylenediamine	48; 15	1:2	THF/diethyl ether	vapour diffusion	none
o-phenylenediamine	40; 16	1:2	DMF/diethyl ether	vapour diffusion	none
phenol	41; 15	1:2	THF/diethyl ether	vapour diffusion	crystals of **5**
phenol	40; 11	1:2	DMF/diethyl ether	vapour diffusion	crystals of **5**
thiourea	100; 23	1:2	THF	Slow evaporation	none
triphenylphosphine oxide (TPPO)	64; 59	1:2	THF	Slow evaporation	none
4-hydroxybenzaldehyde	63; 22	1:2	THF	Slow evaporation	none

Table S10 Summary of co-crystallisation experiments with **6**.

Co-crystal former	Quantity (6; co-former) /mg	Mole ratio (6: co-former)	Solvent system	Crystallisation technique	Product
iodopentafluorobenzene	52; 41	1:3	DCM	Slow evaporation	none
bromopentafluorobenzene	53; 34	1:3	DMSO	Slow evaporation	crystals of **6**
hexakis(4-iodophenoxy)-cyclotriphosphazene	29; 59	1:1	DMSO/chloroform	Layered	none
hexakis(4-bromophenoxy)-cyclotriphosphazene	36; 54	1:1	DMSO/chloroform	Layered	crystals of **11**
none	50	-	DMSO	Slow evaporation	crystals of **6**

Table S11 Summary of co-crystallisation experiments with **7**. The first four crystallisations in the table were carried out *via* slow evaporation, and the rest listed in the table were carried out by layering two solutions.

Co-crystal former	Mole ratio (7: co-former)	Quantity (7: co-former) /mg	Solvent	Product
iodopentafluorobenzene	1:2	52:51	chloroform	none
bromopentafluorobenzene	1:2	51:34	chloroform	none
hexakis(4-iodophenoxy)-cyclotriphosphazene	1:1	28:50	chloroform	crystals of **12**
hexakis(4-bromophenoxy)-cyclotriphosphazene	1:1	31:54	chloroform	none
trimesic acid	1:2	52:32	chloroform/THF	none
terephthalic acid	1:2	51:27	chloroform/DMF	co-crystal **7**
fumaric acid	1:3	31:21	THF/DMF	none
pamoic acid	1:3	32:51	THF/DMF	none
boric acid	1:3	33:13	THF/DMF	none
2-aminopyridine	1:3	32:15	THF/DMF	none
urea	1:3	30:12	THF/acetonitrile	urea
adipic acid	1:3	31:14	chloroform/DMF	none
tartaric acid	1:3	30:17	chloroform/DMF	none
maleic acid	1:3	32:10	chloroform/DMF	Fumaric acid /1,4'-bipyridin-1-ium-4-olate co-crystal
citric acid	1:3	33:17	chloroform/DMF	none
succinic acid	1:3	32:13	chloroform/DMF	succinic acid/4,4'-bipyridyl-1-oxide co-crystal
trimesic acid	1:3	33:24	chloroform/DMF	none

Table S11 (continued)

Co-crystal former	Mole ratio (7: co-former)	Quantity (7: co-former) /mg	Solvent	Product
malic acid	1:3	31:15	chloroform/DMF	none
pamoic acid	1:3	31:33	chloroform/DMF	known SIQCIF
fumaric acid	1:3	34:12	chloroform/DMF	none
isophthalic acid	1:3	37:16	chloroform/DMF	none

Table S12 Summary of crystallisation experiments with **8** in a range of solvents and with a series of potential co-crystal formers.

Co-crystal former	Quantity (8; co-former) /mg	Mole ratio (8: co-former)	Solvent system	Crystallisation technique	Product
p-aminobenzoic acid	45; 43	1:6	THF	slow evaporation	none
2-aminoterephthalic acid	50; 56	1:6	THF	slow evaporation	none
3,5-dinitrobenzoic acid	44; 64	1:6	THF	slow evaporation	3,5-dinitrobenzoic acid
phenol	45; 34	1:6	THF	slow evaporation	none
o-phenylene diamine	59; 34	1:6	THF	slow evaporation	none
2,6-dipicolinic acid	46; 52	1:6	DMF	slow evaporation	none
pyridine	46	excess	THF	slow evaporation	none
4,4'-bipyridine	45; 51	1:6	THF	slow evaporation	4,4-bipyridine hydrate
4,4'-trimethylene dipyridine	42; 64	1:6	THF	slow evaporation	none
3,4-lutidine	51; 42	1:6	THF	slow evaporation	none
3,5-lutidine	55; 41	1:6	THF	slow evaporation	none
2,3-lutidine	48; 45	1:6	THF	slow evaporation	none
2,5-lutidine	44; 36	1:6	THF	Slow evaporation	none
2,4-lutidine	44; 38	1:6	THF	slow evaporation	none
2,6-lutidine	44; 35	1:6	THF	Slow evaporation	none
2-picoline	42; 29	1:6	THF	slow evaporation	none
3-picoline	49; 28	1:6	THF	Slow evaporation	none
4-picoline	43; 31	1:6	THF	Slow evaporation	none
3,4-lutidine	54; 47	1:6	Methanol/ hexane	Layering	none

Table S12 (continued)

Co-crystal former	Quantity (8; co-former) /mg	Mole ratio (8: co-former)	Solvent system	Crystallisation technique	Product
3,5-lutidine	55; 45	1:6	Methanol/ hexane	Layering	none
2,4-lutidine	54; 45	1:6	Methanol/ hexane	Layering	none
2,6-lutidine	52; 45	1:6	Methanol/ hexane	layering	none
3,4-lutidine	50; 44	1:6	DMF	Slow evaporation	none
3,5-lutidine	55; excess	-	DMF	Slow evaporation	none
2,3-lutidine	58; excess	-	-	Slow evaporation	none
2,4-lutidine	68; 55	1:6	DMF	Slow evaporation	none
2,6-lutidine	53; 41	1:6	DMF	Slow evaporation	none
2-picoline	neat	-	-	Slow evaporation	none
3-picoline	neat	-	-	Slow evaporation	none
4-picoline	neat	-	-	Slow evaporation	none
pyridine	neat	-	-	Slow evaporation	none
2,6-diaminopyridine	53; 41	1:6	DMF	slow evaporation	none
piperazine	71; 50	1:6	THF	slow evaporation	none
2,3-lutidine	52; 42	1:6	DMF	Slow evaporation	none
2,5-lutidine	58; 46	1:6	DMF	Slow evaporation	none
3,5-lutidine	52; 42	1:6	DMF	Slow evaporation	none
2-picoline	50; 38	1:6	DMF	Slow evaporation	none
3-picoline	54; 34	1:6	DMF	Slow evaporation	none
4-picoline	50; 46	1:6	DMF	Slow evaporation	none
pyridine	56; 35	1:6	DMF	Slow evaporation	none
4,4'-bipyridine	58; 60	1:6	DMF	Slow evaporation	none
4,4'-trimethylene dipyridine	50; 90	1:6	DMF	Slow evaporation	none
piperazine	57; 39	1:6	DMF	Slow evaporation	none
2,6-diaminopyridine	65; 50	1:6	THF	Slow evaporation	none
thiourea	101; 58	1:6	THF	Slow evaporation	none

Table S13 Summary of crystallisation experiments with **9** in a range of solvents and with a series of potential co-crystal formers.

Co-former	Quantity (9; co-former) /mg	Mole ratio (9: co-former)	Solvent system	Crystallisation technique	Product
imidazole	100; 25	1:3	THF	Inert (under N_2)	none
benzimidazole	109; 46	1:3	THF	Inert (under N_2)	none
4,4'-bipyridine	118; 57	1:3	THF	Inert (under N_2)	none
2-aminopyridine	106; 35	1:3	THF	Inert (under N_2)	none
urea	98; 22	1:3	THF/acetonitrile	Inert (under N_2)	none
pyridine	118; 34	1:3	THF	Inert (under N_2)	none
3,4-lutidine	118; 40	1:3	THF	Inert (under N_2)	none
4-picoline	99; 32	1:3	THF	Inert (under N_2)	none
2,6-diaminopyridine	120; 41	1:3	THF	Inert (under N_2)	none
benzonitrile	161	As solvent	-	Inert (under N_2)	none
2-cyanopyridine	135; 56	1:3	THF	Inert (under N_2)	crystals of **9α**
3-cyanopyridine	109; 55	1:3	THF	Inert (under N_2)	none
4-cyanopyridine	140; 44	1:3	THF	Inert (under N_2)	none
fluorophenol	50; 37	1:3	Acetonitrile/DCM	Slow evaporation	none
1,4-difluorobenzene	48; 22	1:3	acetonitrile	Slow evaporation	none
1,3-dibromobenzene	48; 48	1:3	acetonitrile	Slow evaporation	none
4-bromobenzonitrile	54; 35	1:3	Acetonitrile/DCM	Slow evaporation	crystals of **9β**
4-chlorotoluene	51; 28	1:3	acetonitrile	Slow evaporation	none
4-iodoaniline	53; 44	1:3	Acetonitrile/DCM	Slow evaporation	none
3-bromopyridine	52; 36	1:3	acetonitrile	Slow evaporation	none
3-bromoanisol	50; 19	1:1	acetonitrile	Slow evaporation	none
α-dibromo-*p*-xylene	51; 23	1:1	Acetonitrile/DCM	Slow evaporation	crystals of **9β**
α-dibromo-*m*-xylene	52; 21	1:1	Acetonitrile/DCM	Slow evaporation	none
α-dibromo-*o*-xylene	51; 18	1:1	Acetonitrile/DCM	Slow evaporation	crystals of **9β**
3-bromobenzotrifluoride	52; 20	1:1	acetonitrile	Slow evaporation	none
1,2-dichlorobenzene	52; 18	1:1	acetonitrile	Slow evaporation	none
imidazole	61; 10	1:3	THF	Slow evaporation	crystals of **9β**
benzimidazole	60; 19	1:3	THF	Slow evaporation	none
4,4'-bipyridine	60; 23	1:3	THF	Slow evaporation	none

Table S13 (continued)

Co-former	Quantity (9; co-former) /mg	Mole ratio (9: co-former)	Solvent system	Crystallisation technique	Product
4,4'-trimethylene dipyridine	64; 35	1:3	THF	Slow evaporation	none
2-aminopyrimidine	61; 17	1:3	THF	Slow evaporation	none
pyridine	62; 19	1:3	THF	Slow evaporation	crystals of **9α**
3,4-lutidine	61; 17	1:3	THF	Slow evaporation	crystals of **9α**
4-picoline	61; 16	1:3	THF	Slow evaporation	crystals of **9α**
benzonitrile	62; 18	1:3	THF	Slow evaporation	none
2-cyanopyridine	62; 22	1:3	THF	Slow evaporation	none
3-cyanopyridine	61; 17	1:3	THF	Slow evaporation	none
4-cyanopyridine	65; 20	1:3	THF	Slow evaporation	none
cobalt(II)acetate	60; 20	1:1	THF/MeOH	Layered	crystals of **9β**
copper(II)acetate	62; 34	1:1	THF/MeOH	Layered	crystals of **9β**

Table S14 Summary of crystallisation experiments with **10** in a range of solvents and with a series of potential co-crystal formers.

Co-former	Quantity (10; co-former) /mg	Mole ratio (10: co-former)	Solvent system	Crystallisation technique	Product
imidazole	56; 12	1:3	THF	Slow evaporation	crystals of **10**
benzimidazole	50; 13	1:3	THF	Slow evaporation	crystals of **10**
α-dibromo-*p*-xylene	51; 30	1:3	THF/DCM	Slow evaporation	none
α-dibromo-*o*-xylene	53; 34	1:3	THF/DCM	Slow evaporation	crystals of **10**
4-bromobenzonitrile	50; 21	1:3	THF/DCM	Slow evaporation	none
3,4-lutidine	53; 14	1:3	DCM	Slow evaporation	none
pyridine	51; 14	1:3	THF	Slow evaporation	none
cobalt(II)acetate	48; 15	1:1	THF/MeOH	Layered	none
copper(II)acetate	54; 12	1:1	THF/MeOH	Layered	none
hexakis(4-fluorophenoxy)cyclo-triphosphazene	28; 24	1:1	THF	Slow evaporation	none
hexakis(4-bromophenoxy)cyclo-triphosphazene	26; 33	1:1	THF	Slow evaporation	none
phosphonitrilic chloride trimer	51; 19	1:1	THF	Slow evaporation	none
4-chlorophenol	57; 16	1:3	THF	Slow evaporation	crystals of **10**
iodopentafluoroben-zene	52; 18	1:1	Chloroform/aceto-nitrile	Vapour diffusion (AcCN)	crystals of **10**
bromopentafluoroben-zene	50;24	1:1	Chloroform/aceto-nitrile	Vapour diffusion (AcCN)	crystals of **10**

Table S15 Summary of crystallisation experiments with **11** in a range of solvents and with a series of potential co-crystal formers.

Co-former	**Amount (11; co-former) in mg**	**Ratio (11: co-former)**	**Solvent system**	**Crystallisation technique**	**Product**
hexakis(4-fluorophenoxy)cyclo-triphosphazene	63; 41	1:1	THF	Slow evaporation	crystals of **11**
hexakis(4-iodophenoxy)-cyclotriphosphazene	65; 78	1:1	THF	Slow evaporation	none
imidazole	62; 10	1:3	THF	Slow evaporation	crystals of **11**
α-dibromo-*p*-xylene	63; 30	1:3	THF/DCM	Slow evaporation	α-dibromo-*p*-xylene
α-dibromo-*o*-xylene	64; 36	1:3	THF/DCM	Slow evaporation	none
4-bromobenzonitrile	63; 29	1:3	THF/DCM	Slow evaporation	crystals of **11**
cobalt(II)acetate	60; 18	1:2	THF/MeOH	Layered	crystals of **11**
copper(II)acetate	60; 12	1:2	THF/MeOH	Layered	crystals of **11**
3,4-lutidine	61; 14	1:3	THF	Slow evaporation	crystals of **11**
pyridine	62; 17	1:3	THF	Slow evaporation	crystals of **11**
5	68; 39	1:1	THF	Slow evaporation	crystals of **11**
phosphonitrilic chloride trimer	65; 18	1:1	THF	Slow evaporation	crystals of **11**
bromopentafluoroben-zene	54; 18	1:1	Chloroform/ acetonitrile	Vapour diffusion (AcCN)	crystals of **11**
iodopentafluorobenzene	52; 14	1:1	Chloroform/ acetonitrile	Vapour diffusion (AcCN)	crystals of **11**
bromopentafluorobenzene	51; 52	1:4	Chloroform/ acetonitrile	Vapour diffusion (AcCN)	crystals of **11**

Table S16 Summary of crystallisation experiments with **12** in a range of solvents and with a series of potential co-crystal formers.

Co-former	Quantity (12; co-former) /mg	Mole ratio (12: co-former)	Solvent system*	Crystallisation technique	Product
4-iodoaniline	61; 32	1:3	DCM	Slow evaporation	crystals of **12**
acetonitrile	59	excess	DCM/ acetonitrile	Slow evaporation	none
4-bromobenzonitrile	62; 26	1:3	DCM	Slow evaporation	crystals of **12**
1,3-dicyanobenzene	62; 19	1:3	DCM	Slow evaporation	crystals of **12**
2-cyanopyridine	59; 16	1:3	DCM	Slow evaporation	none
3-cyanopyridine	61; 16	1:3	DCM	Slow evaporation	none
4-cyanopyridine	65; 22	1:3	DCM	Slow evaporation	crystals of **12**
4-iodobenzonitrile	64; 31	1:3	DCM	Slow evaporation	none
benzonitrile	63; 16	1:3	DCM	Slow evaporation	crystals of **12**
nitrobenzene	66; 26	1:3	DCM	Slow evaporation	none
o-tolunitrile	65; 21	1:3	DCM	Slow evaporation	none
m-tolunitrile	61; 22	1:3	DCM	Slow evaporation	none
p-tolunitrile	61; 19	1:3	DCM	Slow evaporation	none
iodophenol	60; 32	1:3	DCM/THF	Slow evaporation	crystals of **12**
1,2-bis(2-pyridyl)ethylene	65; 25	1:3	DCM/THF	Slow evaporation	crystals of **12**
4,4'-diiodobiphenyl	67; 51	1:3	DCM	Slow evaporation	none
1,4-diiodobenzene	64; 46	1:3	DCM	Slow evaporation	none
2-iodopropane	62; 24	1:3	DCM	Slow evaporation	none
propionitrile	64; 13	1:3	DCM	Slow evaporation	none
terephthalonitrile	64; 19	1:3	DCM/ acetonitrile	Slow evaporation	crystals of **12**
4-(4-fluorophenyl)benzonitrile	62; 26	1:3	DCM	Slow evaporation	none
hexakis(4-fluorophenoxy)cyclotri-phosphazene	66; 38	1:1	Chloroform	Slow evaporation	crystals of **12** and **9**
iodopentafluorobenzene	51; 11	1:1	Chloroform/ acetonitrile	Vapour diffusion (AcCN)	crystals of **12**
iodopentafluorobenzene	51; 50	1:4	Chloroform/ acetonitrile	Vapour diffusion (AcCN)	crystals of **12**
bromopentafluorobenzene	50; 24	1:1	Chloroform/ acetonitrile	Vapour diffusion (AcCN)	crystals of **12**

*These crystallisations were also repeated in chloroform

Table S17 Crystallisations from the melt with **9**, **10**, **11** and **12** in a 1:1 mole ratio

Compound 1	**Compound 2**	**Amount (cmp 1; cmp 2) /mg**	**Method**
hexakis(4-fluorophenoxy)-cyclotriphosphazene	hexakis(4-chlorophenoxy)-cyclotriphosphazene	46; 52	Ground together & melted
hexakis(4-fluorophenoxy)-cyclotriphosphazene	hexakis(4-bromophenoxy)-cyclotriphosphazene	45; 68	Ground together & melted
hexakis(4-fluorophenoxy)-cyclotriphosphazene	hexakis(4-iodophenoxy)-cyclotriphosphazene	42; 82	Ground together & melted
hexakis(4-chlorophenoxy)-cyclotriphosphazene	hexakis(4-bromophenoxy)-cyclotriphosphazene	39; 53	Ground together & melted
hexakis(4-chlorophenoxy)-cyclotriphosphazene	hexakis(4-iodophenoxy)-cyclotriphosphazene	41; 66	Ground together & melted
hexakis(4-iodophenoxy)-cyclotriphosphazene	hexakis(4-bromophenoxy)-cyclotriphosphazen	51; 41	Ground together & melted

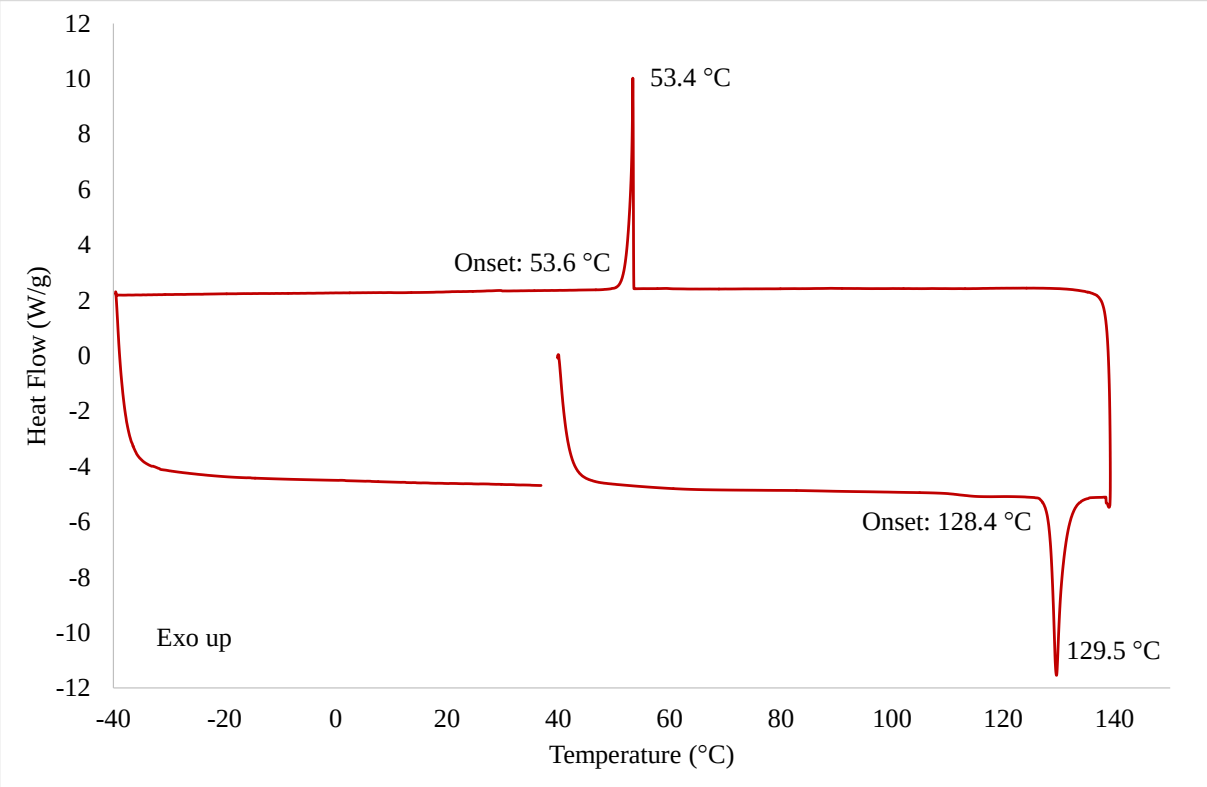


Figure S6 DSC analysis of the monoclinic form of hexakis(4-fluorophenoxy)cyclotriphosphazene (**9**), with a melt at 128.4 °C and a recrystallization event upon cooling at 53.6 °C. This structure undergoes single-crystal to single-crystal polymorphic transitions where **9α** (the monoclinic *P* form) converts to **9γ** between 115 and 125 °C before melting.

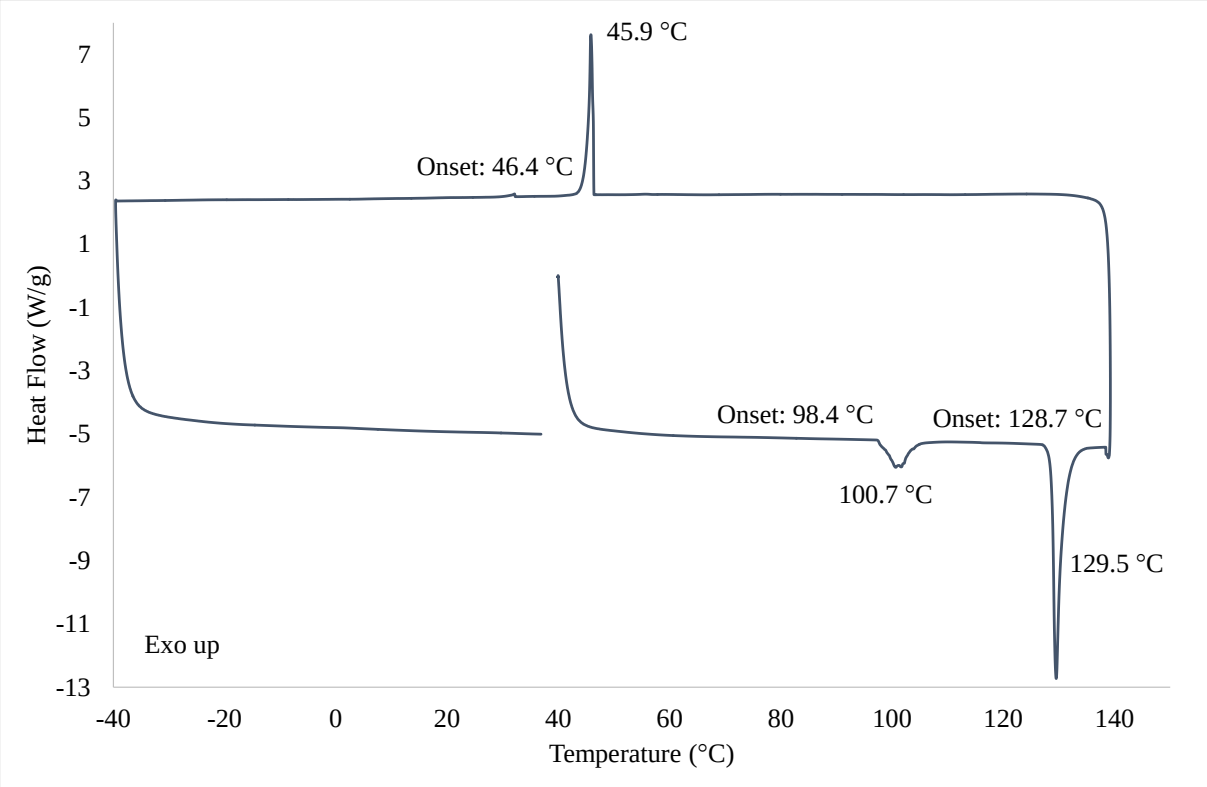


Figure S7 DSC analysis of the triclinic form of hexakis(4-fluorphenoxy)cyclotriphosphazene (**9**). The triclinic form (**9β**) converts to **9γ** around 100 °C before the melt at 129.5 °C.

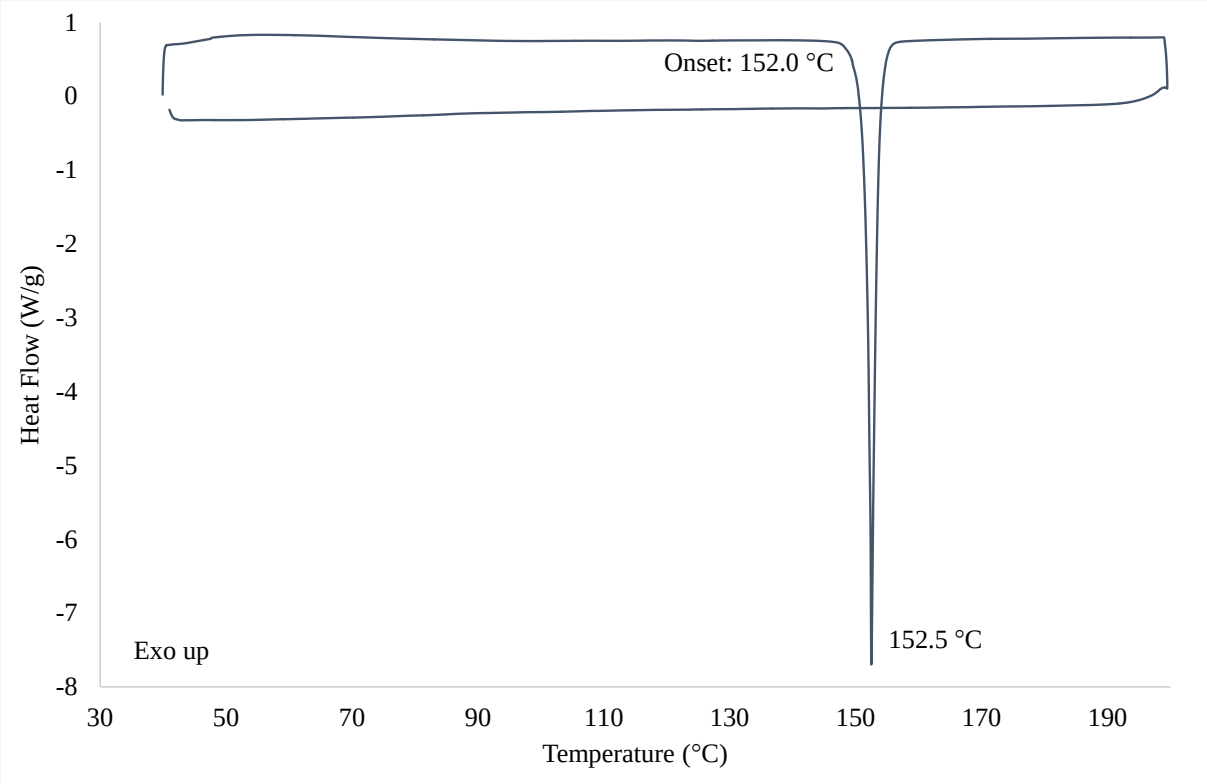


Figure S8 DSC analysis of hexakis(4-chlorophenyl)cyclotriphosphazene (**10**), with a melt occurring at 152.0 °C.

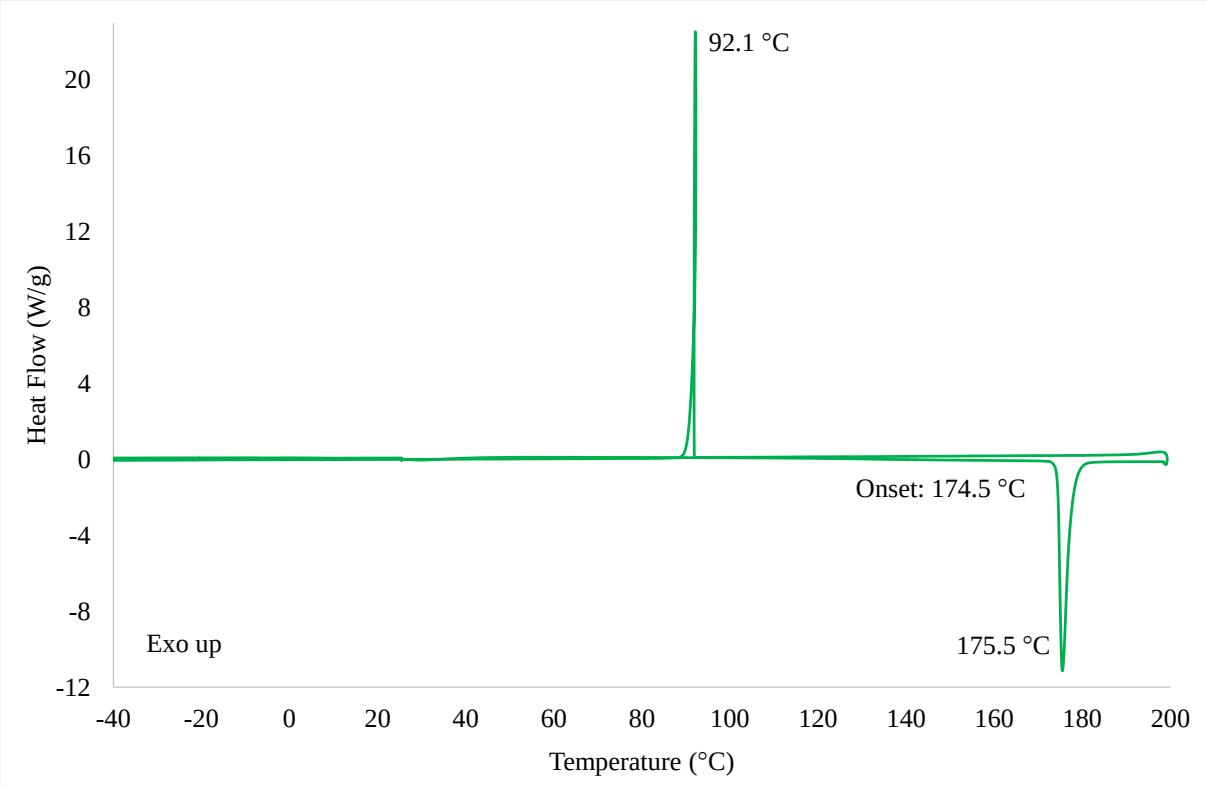


Figure S9 DSC analysis of hexakis(4-bromophenyl)cyclotriphosphazene (**11**), with a melt occurring at 174.5 °C and a recrystallization event upon cooling at 92.1 °C.

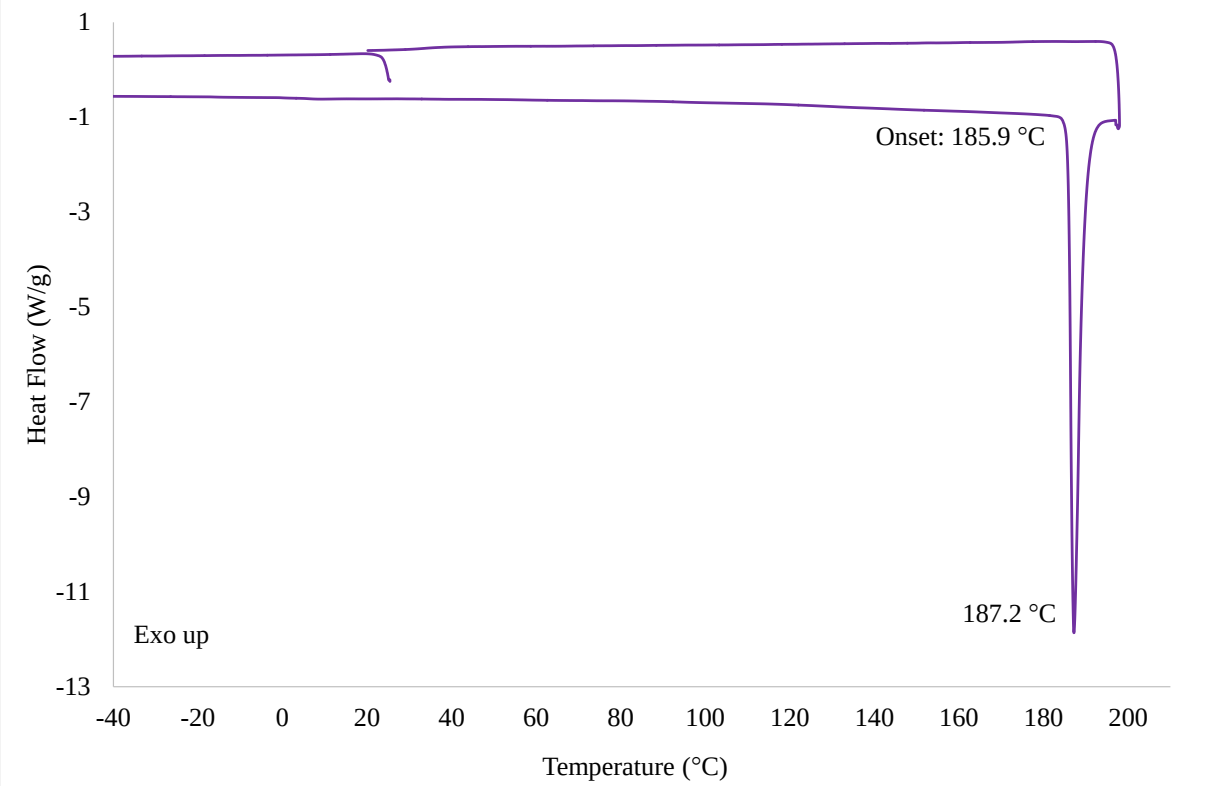


Figure S10 DSC analysis of hexakis(4-iodophenyl)cyclotriphosphazene (**12**), with a melt at 185.9 °C.

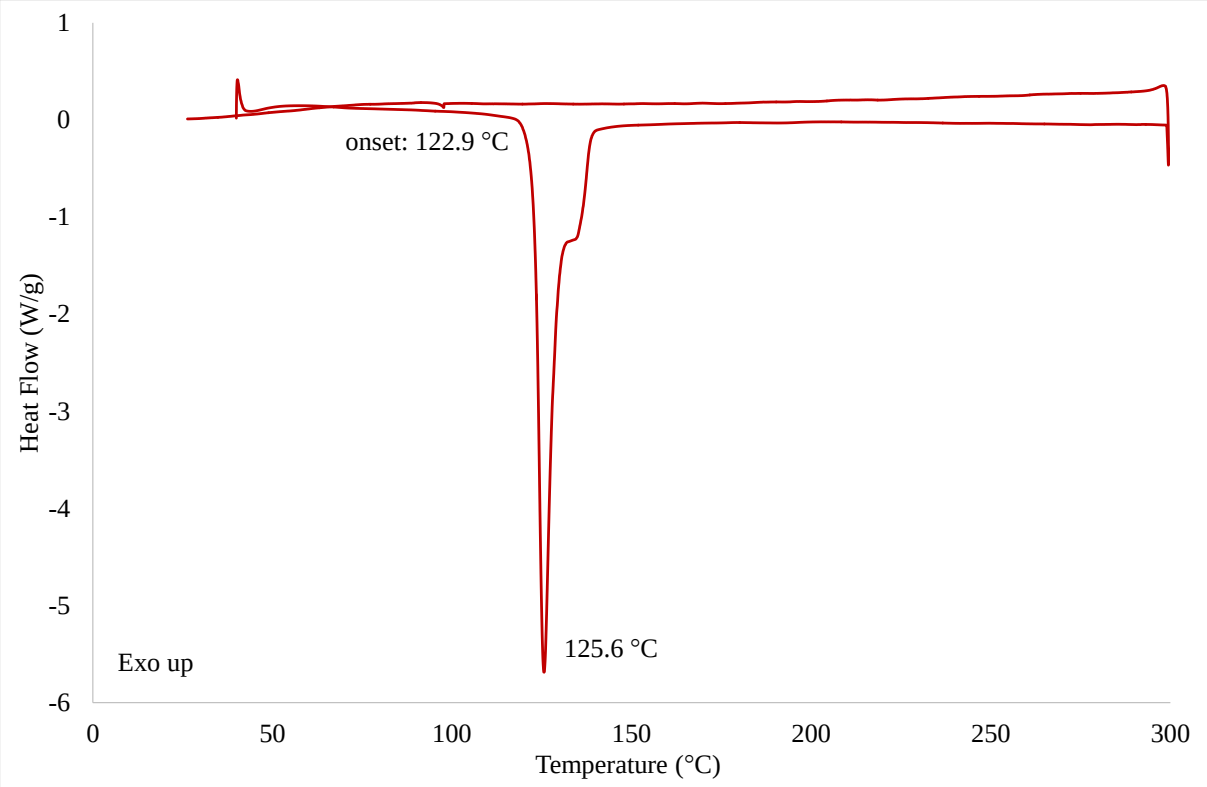


Figure S11 DSC analysis of the melt product (**9/10**) of the fluoro and chloro derivatives. Melting occurs before the melting point of the fluorophenoxy derivative (129 °C).

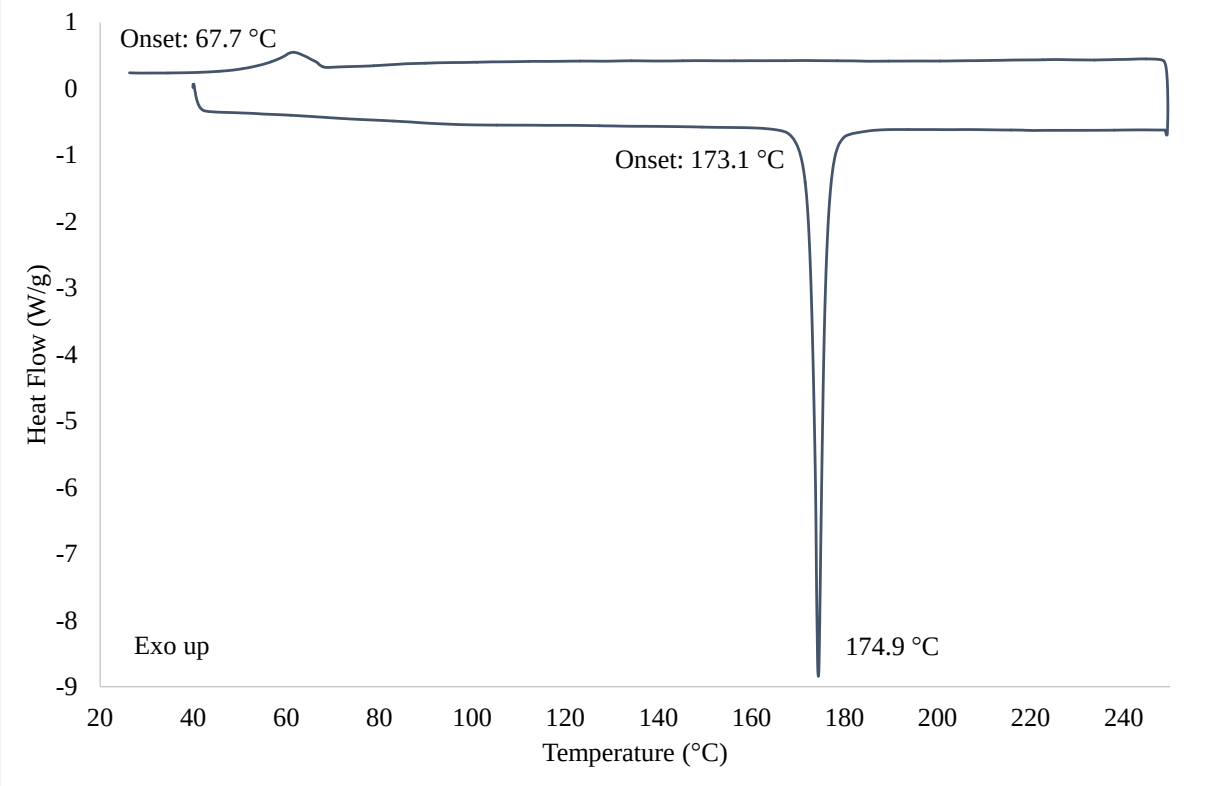


Figure S12 DSC analysis of the product of **11** and **12**. The melting point of **11**/**12** is lower than that of both the reagents.

Synthesis of 1-12

All chemicals were purchased from Sigma-Aldrich and used without further purification. THF, diethylether and toluene were distilled over sodium sand or wire with benzophenone as indicator, under an atmosphere of dry nitrogen. DCM and acetonitrile were distilled over dried calcium hydride under an atmosphere of dry nitrogen. Acetone and *n*-hexane were distilled over dried calcium chloride under nitrogen.

^{1}H and ^{31}P NMR spectra were obtained using a 300 MHz Varian VNMRS or a 400 MHz Varian Unity Inova. Chemical shift values are in ppm and were referenced to either chloroform-*d* or DMSO-d_6. Data for ^{1}H spectra are reported as chemical shift (δ ppm) (integration, multiplicity, coupling constant (Hz)). H_3PO_4 was used as an external standard for ^{31}P NMR.

All reactions were performed under an atmosphere of dry nitrogen unless otherwise stated.

Tris(1,3-diaminopropane)cyclotriphosphazene (1)[1]

$N_3P_3Cl_6$ (0.5 g,1.44 mmol) was dissolved in 50 ml of a 7:3 mixture of *n*-hexane:DCM. To this mixture, 0.8 ml (8.64 mmol) 1,3-diaminopropane was added. The reaction mixture was refluxed for 4 hours, after which the solution was cooled and filtered and the solvent removed under reduced pressure. The resultant white powder was further purified by recrystallisation from methanol. Yield: 62% (0.313 g, 0.89 mmol).

^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 1.53 (2H, m), 3.04 (4H, m), 3.48 (2H, s), ^{31}P NMR (DMSO-d_6, 400 MHz, H_3PO_4): δ ppm 13.86 (d), 20.45 (t).

Crystals of **1** were also grown from a THF/hexane solution. This proved to be the known hydrate.[1a]

4,4,6,6-Tetrachloro-2,2-(biphenyl-2,2'-dioxy)cyclotriphosphazene (2)[2]

A mixture of $N_3P_3Cl_6$ (1.018 g, 2.88 mmol), 2,2'-biphenol (0.543 g, 2.88 mmol) and K_2CO_3 (2.013 g, 14.4 mmol) were stirred together in 40 ml acetone at room temperature for 30 minutes. The volatiles were evaporated *in vacuo* and the residue extracted with 4 x 15 ml DCM. The solvent was evaporated to give a white solid, which was recrystallised from DCM/petroleum ether. Yield: 80% (1.071 g, 2.32 mmol). Mp.: 181 – 189 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.57 (2H, d, *J* = 7.62 Hz), 7.49 (2H, t, *J* = 7.42 Hz), 7.41 (2H, t, *J* = 7.62 Hz), 7.33 (2H, d, 8.01 Hz), ^{31}P NMR ($CDCl_3$, 400 MHz, H_3PO_4): δ ppm 21.87 (d, Cl_2), 9.74 (t, $C_{12}O_2H_8$).

2,2-Dichloro-4,4,6,6-bis[spiro(2',2''-dioxy-1',1''-biphenylyl]cyclotriphosphazene (3)[3]

$N_3P_3Cl_6$ (2 g, 5.75 mmol), biphenyl-2,2'-diol (2.14 g, 11.51 mmol) and K_2CO_3 (3.98 g, 28.77 mmol) were mixed in 20 ml acetone at 0 °C. The reaction mixture was stirred at room temperature for 24 hours, and then the solvent was removed *in vacuo*. The product was extracted by washing with 15 ml of DCM four times, filtering each time with a cannula filter. The solvent was then removed under vacuum, yielding a white powder. Yield: 86% (2.847 g, 4.96 mmol). Mp.: 268 – 275 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 7.55 (4H, d, *J* = 7.63 Hz), 7.46 (4H, d, *J* = 7.63 Hz), 7.36 (8H, m), ^{31}P NMR ($CDCl_3$, 300 MHz, H_3PO_4): δ ppm 19.79 (d, $C_{12}O_2H_8$), 29.19 (dd, Cl_2).

Tris(2,2'-dioxybiphenyl)cyclotriphosphazene (4)[4]

$N_3P_3Cl_6$ (1.003 g, 2.88 mmol), 2,2'-biphenol (1.815 g, 9.66 mmol) and K_2CO_3 (3.010 g, 21.8 mmol) were refluxed for 7 hours in 140 ml acetone. The solvent was evaporated *in vacuo* and the residue washed with 100 ml water, 100 ml aqueous NaOH (0.5 M), 2 x 50 ml water, 50 ml ethanol and 50 ml ether. The white product was dried under vacuum. Yield: 75% (1.278 g, 1.86 mmol). Mp.: >350 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.52 (2H, d, J = 7.62 Hz), 7.41 (4H, m), 7.33 (2H, t, J = 7.642 Hz), ^{31}P NMR ($CDCl_3$, 400 MHz, H_3PO_4): δ ppm 26.27 (s).

2,2-Bis(4-formylphenoxy)-4,4,6,6-bis[spiro(2',2''-dioxy-1',1''-biphenylyl]cyclotriphosphazene (5)[3]

Compound **3** (2 g, 3.48 mmol), 4-hydroxybenzaldehyde (0.854 g, 6.96 mmol) and K_2CO_3 (2.663 g, 19.28 mmol) were added to 20 ml THF at 0 °C. The mixture was refluxed for 5 hours and the solvent removed under vacuum. The resulting solid was extracted with DCM (4 x 10 ml), and the solvent subsequently removed under vacuum. The product was recrystallised from acetone. Yield: 72% (1.881 g, 2.52 mmol). Mp.: 220 – 224 °C

^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 7.07 (2H, d, J = 7.80 Hz), 7.31 – 7.41 (4H, m), 7.54 (4H, t, J = 8.58 Hz), 7.96 (2H, d, 8.19 Hz), 10.01 (1H, s) ^{31}P NMR ($CDCl_3$, 300 MHz, H_3PO_4): δ ppm 9.62 – 11.69 (tt), 25.59 – 26.71 (dt).

Hexakis(4-cyanophenoxy)cyclotriphosphazene (6)[5]

A mixture of 4-cyanophenol (2.071 g, 17.28 mmol) and K_2CO_3 (4.804 g, 34.56 mmol) was prepared in 80 ml THF. $N_3P_3Cl_6$ (1.030 g, 2.88 mmol) in 15 ml THF was added dropwise to this mixture. The reaction mixture was refluxed for 6 hours with vigorous stirring. The solvent was removed *in vacuo* and the residue dispersed in 100 ml water. The resultant white solid was separated by filtration and allowed to dry. Yield: 94 % (2.284 g, 2.707 mmol). Mp.: 263 – 265 °C.

^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 7.16 (2H, d, 8.79 Hz), 7.82 (2H, d, 8.79 Hz), ^{31}P NMR (DMSO-d_6, 400 MHz, H_3PO_4): δ ppm 8.51 (s).

Hexakis(4-pyridyloxy)cyclotriphosphazene (7)[6]

4-hydroxypyridine (0.826 g, 8.64 mmol) and K_2CO_3 (1.818 g, 12.96 mmol) were added to 50 ml THF. $N_3P_3Cl_6$ (0.503 g, 1.44 mmol) was added to this mixture, which was then stirred for two and a half days at room temperature, after which it was refluxed for approximately 6 hours. The solvent was removed under vacuum and the residue washed with 100 ml water. The product was isolated by filtration and dried *in vacuo* to yield a light yellow product. Yield: 89% (0.897 g, 1.28 mmol). Mp.: 163 – 165 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 6.93 (2H, d, 6.44 Hz), 8.50 (2H, d, 6.25 Hz), ^{31}P NMR ($CDCl_3$, 400 MHz, H_3PO_4): δ ppm 7.30 (s).

Hexakis(4-hydroxyphenoxy)cyclotriphosphazene (8)[7]

Hexakis(4-methoxyphenoxy)cyclotriphosphazene

A suspension of sodium 4-methoxyphenoxide was prepared in 20 ml dry THF by allowing 4-methoxyphenol (4.274 g, 34.5 mmol) to react with NaH (1.385 g as a 60 % dispersion in mineral oil; equivalent to 0.828 g, 34.5 mmol pure NaH). The NaH was washed with dry petroleum ether to remove the mineral oil prior to use. A solution of $N_3P_3Cl_6$ (2 g, 5.75 mmol) in 20 ml THF was added dropwise to this suspension. On complete addition of the phosphonitrilic chloride trimer, the reaction mixture was refluxed for 24 hours with stirring. The reaction mixture was cooled and washed with 100 ml water in order to precipitate the product as a white powder. Yield: 82% (4.136 g, 4.733 mmol). Mp.: 105 – 106 °C

^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 3.72 (3H, s), 6.77 (4H, s)

Hexakis(4-hydroxyphenoxy)cyclotriphosphazene (**8**)

Hexakis(4-methoxyphenoxy)-cyclotriphosphazene (3 g, 3.43 mmol) was dissolved in 30 ml DCM. A solution of BBr_3 (2 ml, 20.6 mmol) in 30 ml DCM was added dropwise to the solution of cyclotriphosphazene. The solution was allowed to stir for 3 hours, after which it was poured carefully into 100 ml of water to precipitate the product. The white precipitate was filtered off, washed with water and dried. Yield: 85% (2.303 g, 2.92 mmol).

^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 6.59 (2H, s), 6.61 (2H, s), ^{31}P NMR (DMSO-d_6, 400 MHz, H_3PO_4): δ ppm 22.32 (s).

Hexakis(4-fluorophenyl)cyclotriphosphazene (9)[8,9]

This synthetic procedure was not performed under inert conditions.

4-fluorophenol (1.94 g, 17.28 mmol) and $N_3P_3Cl_6$ (0.998 g, 2.88 mmol) were dissolved in 60 ml acetone. K_2CO_3 (4.797 g, 120.96 mmol) was added to this mixture, and the reaction mixture was refluxed for 12 hours. The precipitate was filtered off, washed with DCM and combined with the filtrate. The solvent was then removed *in vacuo*. The white powder thus obtained was recrystallised from methanol. Yield: 65% (3.131 g, 3.91 mmol). Mp. 129 °C

^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 6.88 (2H, s), 6.9 (2H, s), ^{31}P NMR ($CDCl_3$, 400 MHz, H_3PO_4): δ ppm 9.86 (s).

Hexakis(4-chlorophenyl)cyclotriphosphazene (10)[8]

4-chlorophenol (2.240 g, 17.28 mmol) and K_2CO_3 (4.793 g, 34.56 mmol) were stirred together in 50 ml acetone. $N_3P_3Cl_6$ (1.004 g, 2.88 mmol) dissolved in 10 ml acetone was added to the mixture, which was then refluxed for 1 day. The solvent was removed under vacuum and the product extracted with DCM. The product was further purified by recrystallisation from acetonitrile. Yield: 76 % (1.982 g, 2.2 mmol). Mp. 152 °C

^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 6.68 (2H, d, 8.20 Hz), 7.17 (2H, d, 8.40 Hz), ^{31}P NMR ($CDCl_3$, 400 MHz, H_3PO_4): δ ppm 9.59 (s).

Hexakis(4-bromophenyl)cyclotriphosphazene (11)[8]

4-bromophenol (3.030 g, 17.28 mmol) and K_2CO_3 (4.779 g, 34.56 mmol) were added to 50 ml acetone. $N_3P_3Cl_6$ (1.011 g, 2.88 mmol) in 10 ml acetone was added to the mixture, which was then refluxed for 2 days. The solvent was removed under vacuum and the product purified by recrystallisation from acetonitrile. Yield: 79 % (2.684 g, 2.3 mmol). Mp. 176.8 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 6.75 (2H, d, 8.79 Hz), 7.33 (2H, d, 8.89 Hz), ^{31}P NMR ($CDCl_3$, 400 MHz, H_3PO_4): δ ppm 9.29 (s).

Hexakis(4-iodophenyl)cyclotriphosphazene (12)[8]

4-iodophenol (3.844 g, 17.28 mmol) and $N_3P_3Cl_6$ (1.007 g, 2.88 mmol) were dissolved in 75 ml acetone. K_2CO_3 (4.821 g, 34.56 mmol) was added to this mixture, which was refluxed for 2 days. The solvent was evaporated under vacuum and the product was extracted with 3 x 20 ml DCM. The product was further purified by recrystallisation from acetonitrile. Yield: 65% (2.702 g, 1.86 mmol). Mp. 187.6 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 6.62 (2H, d, J = 8.79 Hz), 7.52 (2H, d, 8.79 Hz), ^{31}P NMR ($CDCl_3$, 400 MHz, H_3PO_4): δ ppm 9.27 (s).

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Lack of co-crystal formation with cyclotriphosphazenes: a cautionary tale

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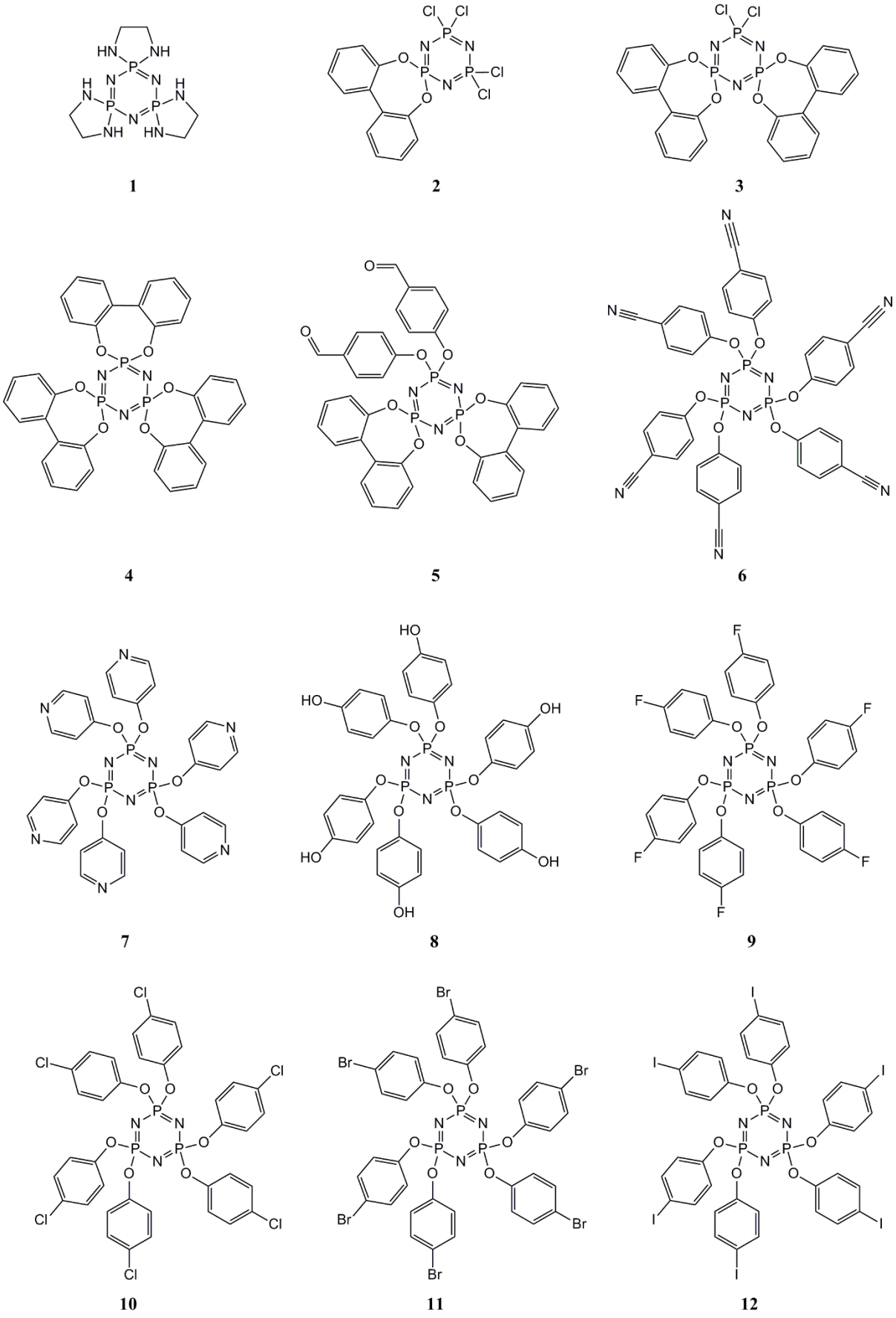
Supporting Information



Scheme S1 The cyclotriphosphazenes investigated in this work.

Co-crystallisation experiments

The components of each crystallisation experiment (see Tables S1, S2, S4, S6, S8-14) were dissolved in the appropriate solvent with gentle heat and stirring. In cases where there were still undissolved particles, the solution was filtered through a non-sterile 33 mm Millex-HV syringe filter unit into a glass vial. All solutions were left to stand at room temperature and crystals were formed either *via* slow evaporation of the solvent, vapour diffusion of one solvent into another or solutions were layered with a second solvent to induce crystal formation at the interface of the two solutions.

Table S1 Co-crystallisation experiments carried out with **1**. All crystallisations were carried out *via* slow evaporation. Crystals obtained were that of the known hydrate of **1** (CSD-COPVAE) or no product was obtained.

Co-former	**Quantity (1; co-former) /mg**	**Mole ratio (1:co-former)**	**Solvent system**	**Product**
isophthalic acid	29; 14	1:1	methanol	none
terephthalic acid	15; 15	1:2	methanol	terephthalic acid
trimesic acid	29; 20	1:1	methanol	none
succinic acid	14; 15	1:3	methanol	none
maleic acid	13; 13	1:3	methanol/THF	none
tartaric acid	13; 12	1:3	methanol	none
2,6-naphthalene dicarboxylic acid	29:18	1:1	methanol	2,6-naphthalene dicarboxylic acid
solvent	-	-	THF	none
solvent	-	-	hexane/THF	known COPVAE
solvent	-	-	DCM	none
solvent	-	-	DMSO	none
solvent	-	-	acetonitrile	known COPVAE
solvent	-	-	methanol	none
solvent	-	-	ethanol	none
solvent	-	-	DMF	none
solvent	-	-	NMP	none
solvent	-	-	chloroform	none

Table S2 Co-crystallisation experiments carried out with **2**. All crystallisations were carried out *via* slow evaporation. In some cases crystals of the starting materials were obtained, otherwise no crystals were obtained.

Co-former	Quantity (2; co-former) /mg	Mole ratio (2:co-former)	Solvent system	Product
DCM	50	As solvent	-	none
benzene	45	As solvent	-	none
toluene	46	As solvent	-	none
chloroform	54	As solvent	-	none
acetonitrile	49	As solvent	-	none
pyridine	48	As solvent	-	none
1,4-dioxane	55	As solvent	-	none
NMP	51	As solvent	-	none
THF	74	As solvent	-	none
DMF	68	As solvent	-	none
isophthalic acid	53; 41	1:2	DCM/THF	none
imidazole	55; 25	1:3	DCM/THF	none
benzimidazole	59; 33	1:3	DCM/THF	benzimidazole hydrate
4,4'-bipyridine	52; 35	1:2	DCM/THF	none
benzonitrile	54	As solvent	-	none
3,4-lutidine	62; 35	1:3	DCM	none

Table S3 Mechanochemical experiments carried out with **2**. Samples were ground by hand in a mortar and pestle for approximately 5 minutes, yielding homogenous powders.

Co-former	Quantity (2; co-former) /mg	Mole ratio (2: co-former)
4,4'-bipyridine	28; 32	1:2
imidazole	56; 24	1:2
benzimidazole	51; 28	1:2
4,4'-bipyridine	62; 21	1:1
imidazole	61; 10	1:1
benzimidazole	64; 15	1:1
piperazine	61; 12	1:1
4,4'-trimethylene dipyridine	65; 30	1:1

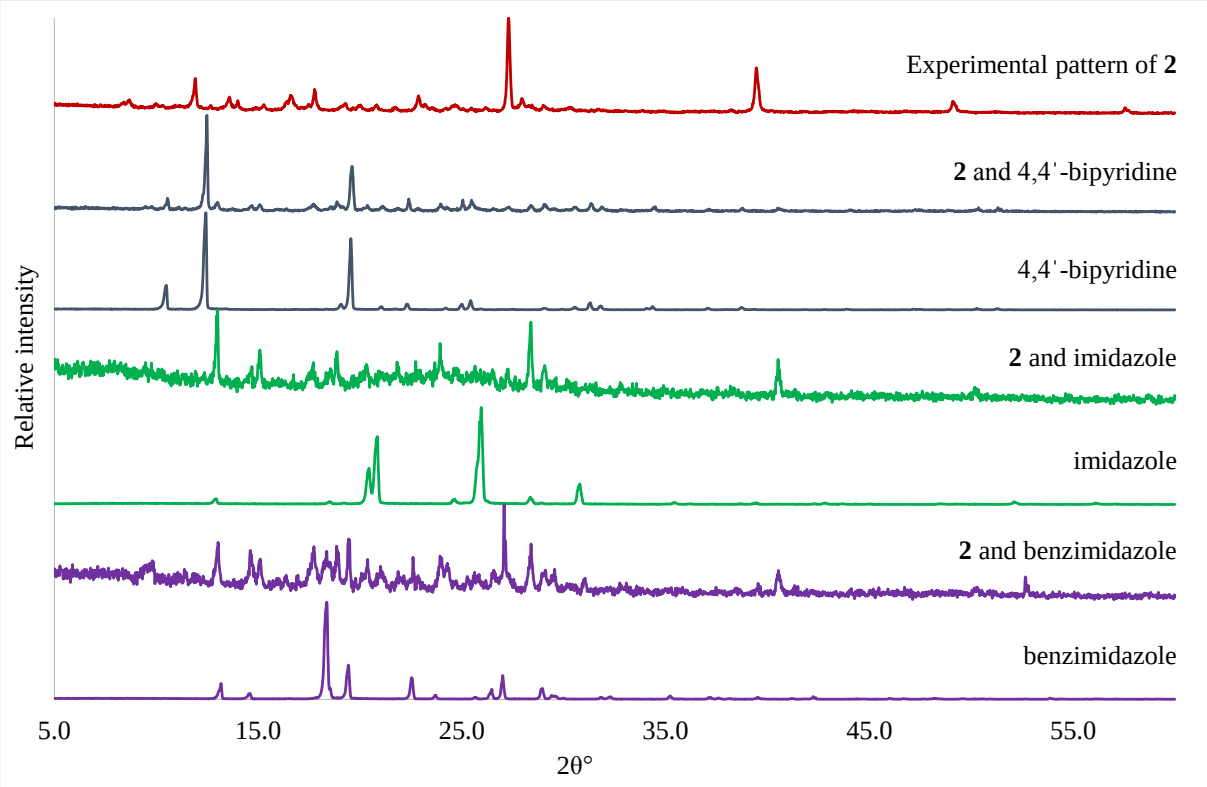


Figure S1 PXRD results of the grinding experiments with **2**. The powder patterns of the products either correspond to that of **2** or the co-crystal former.

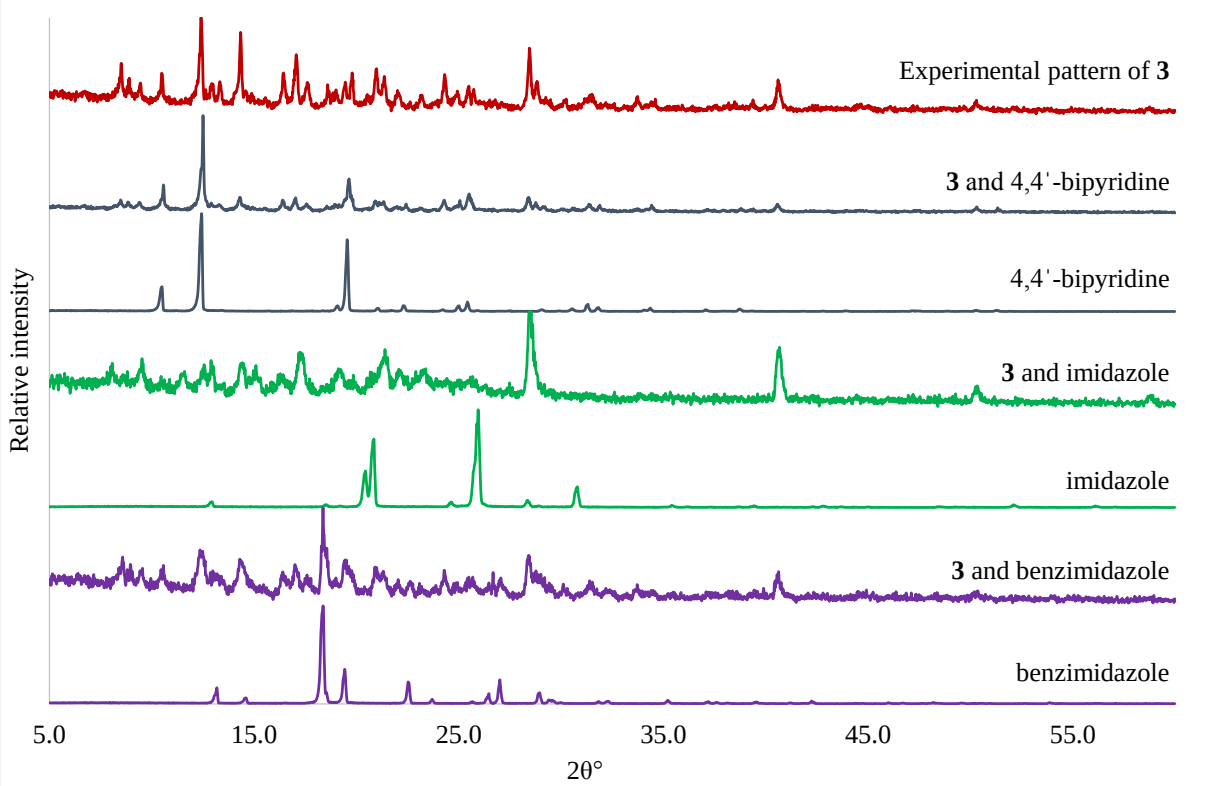


Figure S2 The PXRD results of the mechanochemical experiments between **3** and 4,4'-bipyridine, imidazole and benzimidazole. In most cases there appears to be an agreement between the patterns of the product and 4,4'-bipyridine, imidazole and benzimidazole.

Table S4 Co-crystallisation experiments carried out with **3**. All crystallisations were carried out *via* slow evaporation. In most cases no crystals were obtained, and in a few cases crystals of the starting materials were obtained.

Co-former	Quantity (3; co-former) /mg	Mole ratio (3: co-crystal former)	Solvent system	Product
4,4'-bipyridine	108; 111	1:3	DCM	none
imidazole	107; 65	1:3	DCM	none
benzimidazole	103; 83	1:3	DCM	benzimidazole hydrate
m-xylene	100	excess	*m*-xylene	none
benzene	59	As solvent	-	none
toluene	60	As solvent	-	Known **3**
DCM	60	As solvent	-	none
chloroform	57	As solvent	-	none
acetonitrile	53	As solvent	-	none
pyridine	52	As solvent	-	none
1,4-dioxane	57	As solvent	-	none
NMP	63	As solvent	-	none
THF	62	As solvent	-	none
DMF	67	As solvent	-	none
isophthalic acid	62; 35	1:2	DCM/THF	none
imidazole	69; 15	1:2	DCM/THF	none
benzimidazole	63; 31	1:2	DCM/THF	none
4,4'-bipyridine	63; 33	1:2	DCM/THF	none

Table S5 Mechanochemical experiments carried out with **3**. Samples were ground by hand in a mortar and pestle for approximately 5 minutes, yielding homogenous powders.

Co-former	Quantity (3; co-former) /mg	Mole ratio (3: co-former)
4,4'-bipyridine	62; 33	1:2
imidazole	61; 14	1:2
benzimidazole	60; 13	1:2

Table S6 Summary of crystallisation experiments with **4** in a range of solvents and with a series of potential co-crystal formers. All crystallisations were carried out *via* slow evaporation. Only one crystal of **4** was obtained.

Co-former	**Quantity (4; co-former) /mg**	**Mole ratio (4: co-former)**	**Solvent system**	**Product**
benzene	58	-	-	none
toluene	61	-	-	none
DCM	60	-	-	known **4**
chloroform	58	-	-	none
pyridine	60	Excess	-	none
acetonitrile	62	-	-	none
dioxane	60	-	-	none
NMP	59	-	-	none
THF	61	-	-	none
DMF	60	-	-	none
m-xylene	60	-	-	none
isophthalic acid	60; 51	1:3	THF	none
imidazole	61; 21	1:3	THF	none
benzimidazole	63; 36	1:3	THF	none
4,4'-bipyridine	62; 48	1:3	THF	none

Table S7 Mechanochemical experiments carried out with **4**. Samples were ground by hand in a mortar and pestle for approximately 5 minutes, yielding homogenous powders.

Co-former	**Quantity (4; co-former) /mg**	**Mole ratio (4: co-former)**
4,4'-bipyridine	61; 20	1:1
imidazole	61; 9	1:1
benzimidazole	64; 14	1:1
piperazine	63; 9	1:1
4,4'-trimethylene dipyridine	63; 28	1:1

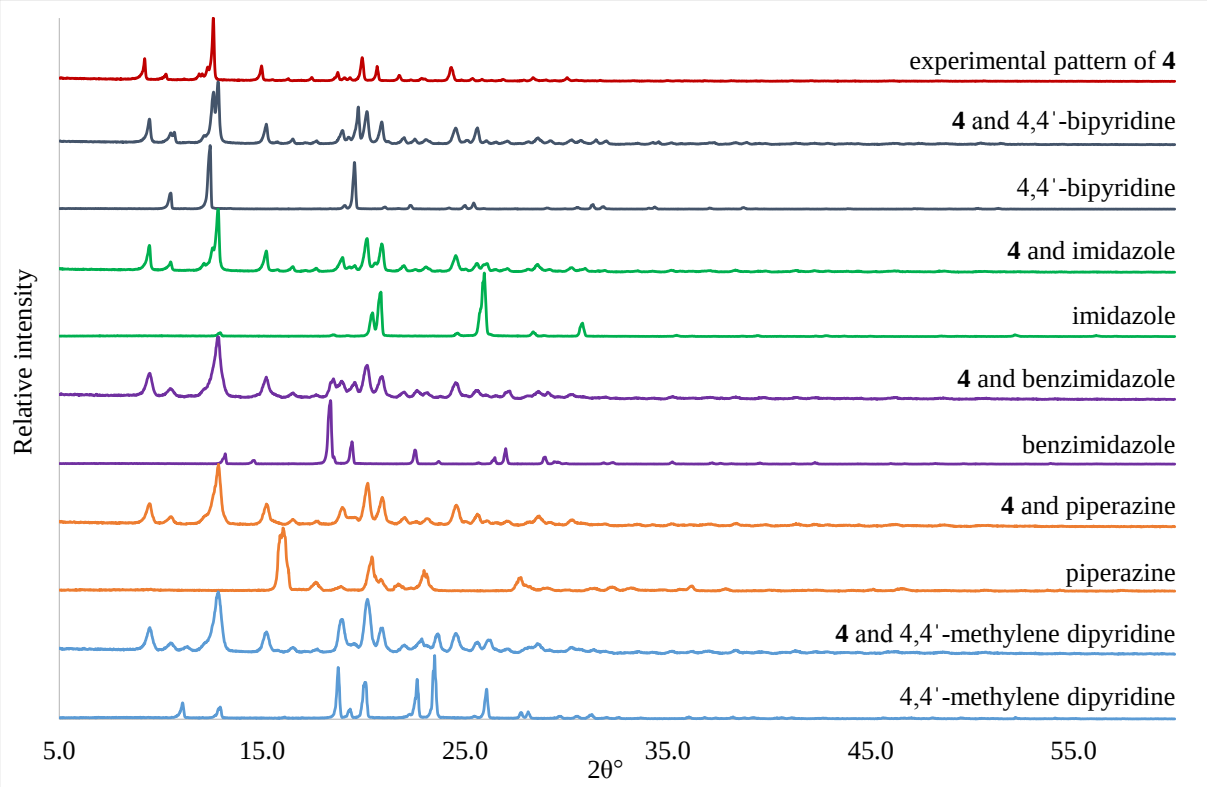


Figure S3 The PXRD results of mechanochemical experiments with **4**. In all cases the product of the grinding experiment corresponds to the powder pattern of **4**, indicating that no co-crystals were formed.

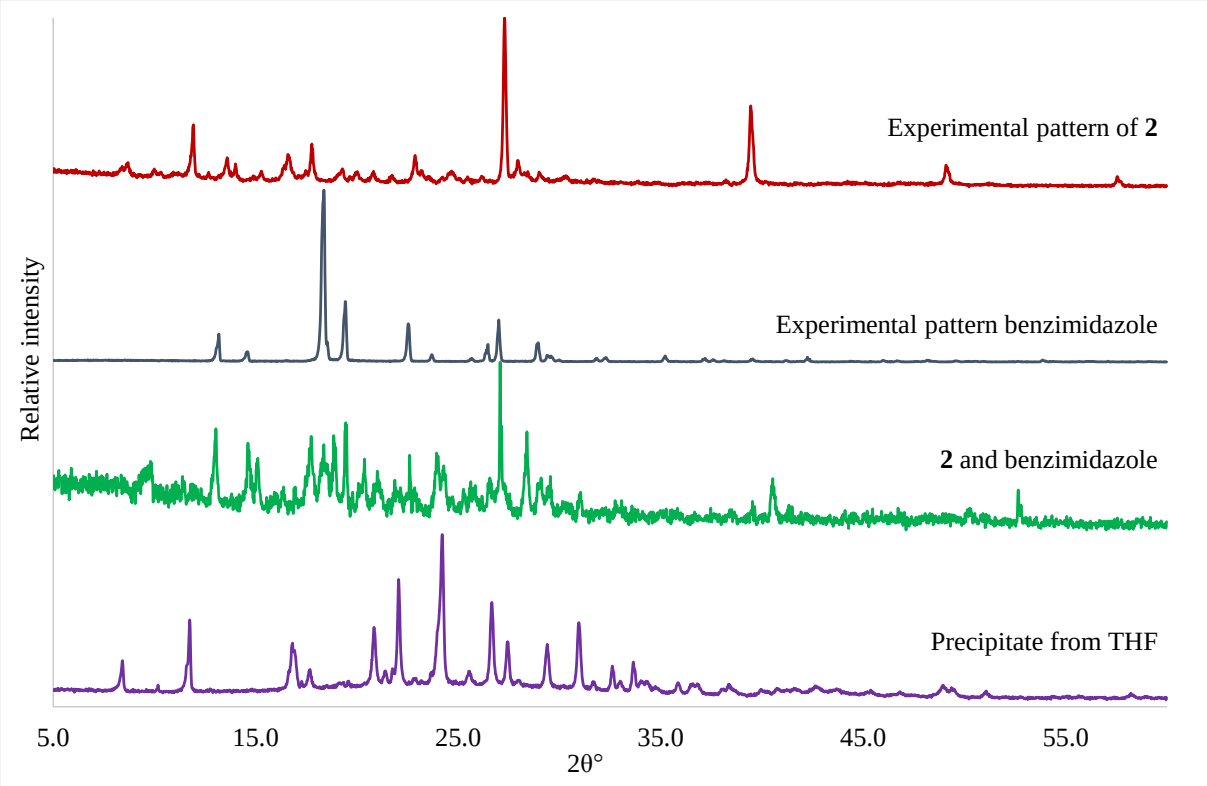


Figure S4 The PXRD results of the precipitate formed when the product of mechanochemical synthesis between **2** and benzimidazole is dissolved in THF.

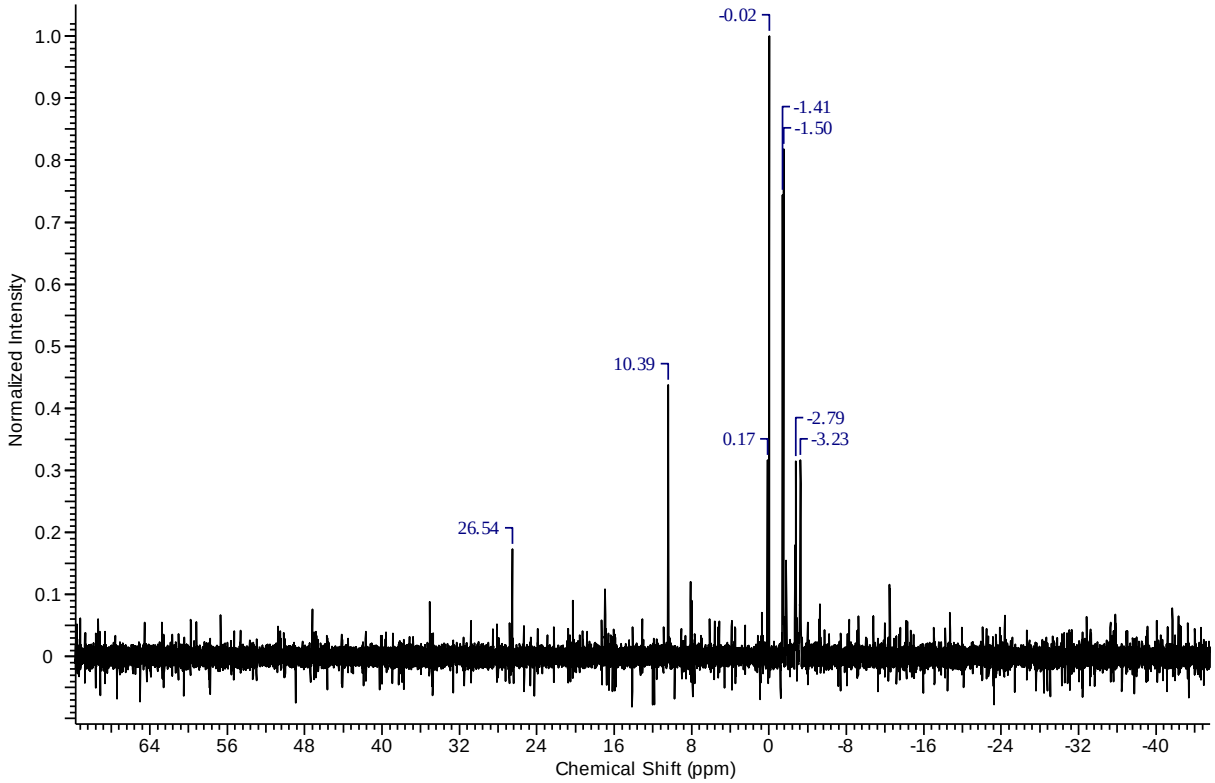


Figure S5 The ^{31}P NMR spectrum of the precipitate formed when the product of mechanochemical synthesis between **2** and benzimidazole is dissolved in THF. Multiple peaks for phosphorous indicates that ring cleavage could have occurred.

Table S8 Summary of crystallisation experiments with **5** from a range of solvents. Approximately 60 mg of **5** was used in each crystallisation.

Solvent system	**Co-crystal former**	**Crystallisation technique**	**Result**
benzene	none	slow evaporation	crystals of **5**
toluene	none	slow evaporation	no crystalline product
methanol	none	slow evaporation	no crystalline product
NMP	none	slow evaporation	no crystalline product
DMSO	none	slow evaporation	no crystalline product
chloroform	none	slow evaporation	no crystalline product
acetone	none	slow evaporation	crystals of **5**

Table S9 Co-crystallisation experiments carried out with **5**.

Co-former	Quantity (5; co-former) /mg	Mole ratio (5: co-former)	Solvent system	Crystallisation technique	Product
pamoic acid	44; 21	1:1	THF	slow evaporation	none
piperazine	40; 6	1:1	THF	slow evaporation	none
2,6-diaminopyridine	41; 7	1:1	THF	slow evaporation,	none
trimesic acid	46; 12	1:1	THF/hexane	layering	trimesic acid and hexane
isophthalic acid	41; 10	1:1	THF/hexane	layering	none
benzonitrile	42; excess	-	THF	slow evaporation	none
2,6-diaminopyridine	40; 12	1:2	THF/diethyl ether	vapour diffusion	none
1,2-diaminoethane	42; 20	1:6	THF/diethyl ether	vapour diffusion	none
1,3-diaminopropane	43; 21	1:6	THF/diethyl ether	vapour diffusion	none
1,4-diaminobutane	42; 15	1:3	THF/diethyl ether	vapour diffusion	none none
1,5-diaminopentane	42; 18	1:3	THF/diethyl ether	vapour diffusion	none
1,6-diaminohexane	41; 15	1:3	THF/diethyl ether	vapour diffusion	none
piperazine	40; 12	1:2	THF/diethyl ether	vapour diffusion	none
p-aminobenzoic acid	40; 15	1:2	DCM/diethyl ether	vapour diffusion	none
p-aminobenzoic acid	40; 17	1:2	DMF/diethyl ether	vapour diffusion	none
2-aminoterephthalic acid	41; 21	1:2	THF/diethyl ether	vapour diffusion	crystals of **5**
2-aminoterephthalic acid	43; 21	1:2	DMF/diethyl ether	vapour diffusion	none
2,6-dipicolinic acid	42; 21	1:2	THF/DCM	vapour diffusion	none
2,6-dipicolinic acid	43; 19	1:2	DMF/ether	vapour diffusion	crystals of **5**
3,5-dinitrobenzoic acid	40; 30	1:2	THF/diethyl ether	vapour diffusion	3,5-dinitrobenzoic acid
3,5-dinitrobenzoic acid	43; 25	1:2	DMF/diethyl ether	vapour diffusion	none
1,6-dihydroxynaphthalene	42; 19	1:2	THF/diethyl ether	vapour diffusion	crystals of **5**
1,6-dihydroxynaphthalene	45; 19	1:2	DMF/diethyl ether	vapour diffusion	crystals of **5**
o-phenylenediamine	48; 15	1:2	THF/diethyl ether	vapour diffusion	none
o-phenylenediamine	40; 16	1:2	DMF/diethyl ether	vapour diffusion	none
phenol	41; 15	1:2	THF/diethyl ether	vapour diffusion	crystals of **5**
phenol	40; 11	1:2	DMF/diethyl ether	vapour diffusion	crystals of **5**
thiourea	100; 23	1:2	THF	Slow evaporation	none
triphenylphosphine oxide (TPPO)	64; 59	1:2	THF	Slow evaporation	none
4-hydroxybenzaldehyde	63; 22	1:2	THF	Slow evaporation	none

Table S10 Summary of co-crystallisation experiments with **6**.

Co-crystal former	Quantity (6; co-former) /mg	Mole ratio (6: co-former)	Solvent system	Crystallisation technique	Product
iodopentafluorobenzene	52; 41	1:3	DCM	Slow evaporation	none
bromopentafluorobenzene	53; 34	1:3	DMSO	Slow evaporation	crystals of **6**
hexakis(4-iodophenoxy)-cyclotriphosphazene	29; 59	1:1	DMSO/chloroform	Layered	none
hexakis(4-bromophenoxy)-cyclotriphosphazene	36; 54	1:1	DMSO/chloroform	Layered	crystals of **11**
none	50	-	DMSO	Slow evaporation	crystals of **6**

Table S11 Summary of co-crystallisation experiments with **7**. The first four crystallisations in the table were carried out *via* slow evaporation, and the rest listed in the table were carried out by layering two solutions.

Co-crystal former	Mole ratio (7: co-former)	Quantity (7: co-former) /mg	Solvent	Product
iodopentafluorobenzene	1:2	52:51	chloroform	none
bromopentafluorobenzene	1:2	51:34	chloroform	none
hexakis(4-iodophenoxy)-cyclotriphosphazene	1:1	28:50	chloroform	crystals of **12**
hexakis(4-bromophenoxy)-cyclotriphosphazene	1:1	31:54	chloroform	none
trimesic acid	1:2	52:32	chloroform/THF	none
terephthalic acid	1:2	51:27	chloroform/DMF	co-crystal **7**
fumaric acid	1:3	31:21	THF/DMF	none
pamoic acid	1:3	32:51	THF/DMF	none
boric acid	1:3	33:13	THF/DMF	none
2-aminopyridine	1:3	32:15	THF/DMF	none
urea	1:3	30:12	THF/acetonitrile	urea
adipic acid	1:3	31:14	chloroform/DMF	none
tartaric acid	1:3	30:17	chloroform/DMF	none
maleic acid	1:3	32:10	chloroform/DMF	Fumaric acid /1,4'-bipyridin-1-ium-4-olate co-crystal
citric acid	1:3	33:17	chloroform/DMF	none
succinic acid	1:3	32:13	chloroform/DMF	succinic acid/4,4'-bipyridyl-1-oxide co-crystal
trimesic acid	1:3	33:24	chloroform/DMF	none

Table S11 (continued)

Co-crystal former	Mole ratio (7: co-former)	Quantity (7: co-former) /mg	Solvent	Product
malic acid	1:3	31:15	chloroform/DMF	none
pamoic acid	1:3	31:33	chloroform/DMF	known SIQCIF
fumaric acid	1:3	34:12	chloroform/DMF	none
isophthalic acid	1:3	37:16	chloroform/DMF	none

Table S12 Summary of crystallisation experiments with **8** in a range of solvents and with a series of potential co-crystal formers.

Co-crystal former	Quantity (8; co-former) /mg	Mole ratio (8: co-former)	Solvent system	Crystallisation technique	Product
p-aminobenzoic acid	45; 43	1:6	THF	slow evaporation	none
2-aminoterephthalic acid	50; 56	1:6	THF	slow evaporation	none
3,5-dinitrobenzoic acid	44; 64	1:6	THF	slow evaporation	3,5-dinitrobenzoic acid
phenol	45; 34	1:6	THF	slow evaporation	none
o-phenylene diamine	59; 34	1:6	THF	slow evaporation	none
2,6-dipicolinic acid	46; 52	1:6	DMF	slow evaporation	none
pyridine	46	excess	THF	slow evaporation	none
4,4'-bipyridine	45; 51	1:6	THF	slow evaporation	4,4-bipyridine hydrate
4,4'-trimethylene dipyridine	42; 64	1:6	THF	slow evaporation	none
3,4-lutidine	51; 42	1:6	THF	slow evaporation	none
3,5-lutidine	55; 41	1:6	THF	slow evaporation	none
2,3-lutidine	48; 45	1:6	THF	slow evaporation	none
2,5-lutidine	44; 36	1:6	THF	Slow evaporation	none
2,4-lutidine	44; 38	1:6	THF	slow evaporation	none
2,6-lutidine	44; 35	1:6	THF	Slow evaporation	none
2-picoline	42; 29	1:6	THF	slow evaporation	none
3-picoline	49; 28	1:6	THF	Slow evaporation	none
4-picoline	43; 31	1:6	THF	Slow evaporation	none
3,4-lutidine	54; 47	1:6	Methanol/ hexane	Layering	none

Table S12 (continued)

Co-crystal former	Quantity (8; co-former) /mg	Mole ratio (8: co-former)	Solvent system	Crystallisation technique	Product
3,5-lutidine	55; 45	1:6	Methanol/ hexane	Layering	none
2,4-lutidine	54; 45	1:6	Methanol/ hexane	Layering	none
2,6-lutidine	52; 45	1:6	Methanol/ hexane	layering	none
3,4-lutidine	50; 44	1:6	DMF	Slow evaporation	none
3,5-lutidine	55; excess	-	DMF	Slow evaporation	none
2,3-lutidine	58; excess	-	-	Slow evaporation	none
2,4-lutidine	68; 55	1:6	DMF	Slow evaporation	none
2,6-lutidine	53; 41	1:6	DMF	Slow evaporation	none
2-picoline	neat	-	-	Slow evaporation	none
3-picoline	neat	-	-	Slow evaporation	none
4-picoline	neat	-	-	Slow evaporation	none
pyridine	neat	-	-	Slow evaporation	none
2,6-diaminopyridine	53; 41	1:6	DMF	slow evaporation	none
piperazine	71; 50	1:6	THF	slow evaporation	none
2,3-lutidine	52; 42	1:6	DMF	Slow evaporation	none
2,5-lutidine	58; 46	1:6	DMF	Slow evaporation	none
3,5-lutidine	52; 42	1:6	DMF	Slow evaporation	none
2-picoline	50; 38	1:6	DMF	Slow evaporation	none
3-picoline	54; 34	1:6	DMF	Slow evaporation	none
4-picoline	50; 46	1:6	DMF	Slow evaporation	none
pyridine	56; 35	1:6	DMF	Slow evaporation	none
4,4'-bipyridine	58; 60	1:6	DMF	Slow evaporation	none
4,4'-trimethylene dipyridine	50; 90	1:6	DMF	Slow evaporation	none
piperazine	57; 39	1:6	DMF	Slow evaporation	none
2,6-diaminopyridine	65; 50	1:6	THF	Slow evaporation	none
thiourea	101; 58	1:6	THF	Slow evaporation	none

Table S13 Summary of crystallisation experiments with **9** in a range of solvents and with a series of potential co-crystal formers.

Co-former	Quantity (9; co-former) /mg	Mole ratio (9: co-former)	Solvent system	Crystallisation technique	Product
imidazole	100; 25	1:3	THF	Inert (under N_2)	none
benzimidazole	109; 46	1:3	THF	Inert (under N_2)	none
4,4'-bipyridine	118; 57	1:3	THF	Inert (under N_2)	none
2-aminopyridine	106; 35	1:3	THF	Inert (under N_2)	none
urea	98; 22	1:3	THF/acetonitrile	Inert (under N_2)	none
pyridine	118; 34	1:3	THF	Inert (under N_2)	none
3,4-lutidine	118; 40	1:3	THF	Inert (under N_2)	none
4-picoline	99; 32	1:3	THF	Inert (under N_2)	none
2,6-diaminopyridine	120; 41	1:3	THF	Inert (under N_2)	none
benzonitrile	161	As solvent	-	Inert (under N_2)	none
2-cyanopyridine	135; 56	1:3	THF	Inert (under N_2)	crystals of **9α**
3-cyanopyridine	109; 55	1:3	THF	Inert (under N_2)	none
4-cyanopyridine	140; 44	1:3	THF	Inert (under N_2)	none
fluorophenol	50; 37	1:3	Acetonitrile/DCM	Slow evaporation	none
1,4-difluorobenzene	48; 22	1:3	acetonitrile	Slow evaporation	none
1,3-dibromobenzene	48; 48	1:3	acetonitrile	Slow evaporation	none
4-bromobenzonitrile	54; 35	1:3	Acetonitrile/DCM	Slow evaporation	crystals of **9β**
4-chlorotoluene	51; 28	1:3	acetonitrile	Slow evaporation	none
4-iodoaniline	53; 44	1:3	Acetonitrile/DCM	Slow evaporation	none
3-bromopyridine	52; 36	1:3	acetonitrile	Slow evaporation	none
3-bromoanisol	50; 19	1:1	acetonitrile	Slow evaporation	none
α-dibromo-*p*-xylene	51; 23	1:1	Acetonitrile/DCM	Slow evaporation	crystals of **9β**
α-dibromo-*m*-xylene	52; 21	1:1	Acetonitrile/DCM	Slow evaporation	none
α-dibromo-*o*-xylene	51; 18	1:1	Acetonitrile/DCM	Slow evaporation	crystals of **9β**
3-bromobenzotrifluoride	52; 20	1:1	acetonitrile	Slow evaporation	none
1,2-dichlorobenzene	52; 18	1:1	acetonitrile	Slow evaporation	none
imidazole	61; 10	1:3	THF	Slow evaporation	crystals of **9β**
benzimidazole	60; 19	1:3	THF	Slow evaporation	none
4,4'-bipyridine	60; 23	1:3	THF	Slow evaporation	none

Table S13 (continued)

Co-former	Quantity (9; co-former) /mg	Mole ratio (9: co-former)	Solvent system	Crystallisation technique	Product
4,4'-trimethylene dipyridine	64; 35	1:3	THF	Slow evaporation	none
2-aminopyrimidine	61; 17	1:3	THF	Slow evaporation	none
pyridine	62; 19	1:3	THF	Slow evaporation	crystals of **9α**
3,4-lutidine	61; 17	1:3	THF	Slow evaporation	crystals of **9α**
4-picoline	61; 16	1:3	THF	Slow evaporation	crystals of **9α**
benzonitrile	62; 18	1:3	THF	Slow evaporation	none
2-cyanopyridine	62; 22	1:3	THF	Slow evaporation	none
3-cyanopyridine	61; 17	1:3	THF	Slow evaporation	none
4-cyanopyridine	65; 20	1:3	THF	Slow evaporation	none
cobalt(II)acetate	60; 20	1:1	THF/MeOH	Layered	crystals of **9β**
copper(II)acetate	62; 34	1:1	THF/MeOH	Layered	crystals of **9β**

Table S14 Summary of crystallisation experiments with **10** in a range of solvents and with a series of potential co-crystal formers.

Co-former	Quantity (10; co-former) /mg	Mole ratio (10: co-former)	Solvent system	Crystallisation technique	Product
imidazole	56; 12	1:3	THF	Slow evaporation	crystals of **10**
benzimidazole	50; 13	1:3	THF	Slow evaporation	crystals of **10**
α-dibromo-*p*-xylene	51; 30	1:3	THF/DCM	Slow evaporation	none
α-dibromo-*o*-xylene	53; 34	1:3	THF/DCM	Slow evaporation	crystals of **10**
4-bromobenzonitrile	50; 21	1:3	THF/DCM	Slow evaporation	none
3,4-lutidine	53; 14	1:3	DCM	Slow evaporation	none
pyridine	51; 14	1:3	THF	Slow evaporation	none
cobalt(II)acetate	48; 15	1:1	THF/MeOH	Layered	none
copper(II)acetate	54; 12	1:1	THF/MeOH	Layered	none
hexakis(4-fluorophenoxy)cyclo-triphosphazene	28; 24	1:1	THF	Slow evaporation	none
hexakis(4-bromophenoxy)cyclo-triphosphazene	26; 33	1:1	THF	Slow evaporation	none
phosphonitrilic chloride trimer	51; 19	1:1	THF	Slow evaporation	none
4-chlorophenol	57; 16	1:3	THF	Slow evaporation	crystals of **10**
iodopentafluoroben-zene	52; 18	1:1	Chloroform/aceto-nitrile	Vapour diffusion (AcCN)	crystals of **10**
bromopentafluoroben-zene	50;24	1:1	Chloroform/aceto-nitrile	Vapour diffusion (AcCN)	crystals of **10**

Table S15 Summary of crystallisation experiments with **11** in a range of solvents and with a series of potential co-crystal formers.

Co-former	**Amount (11; co-former) in mg**	**Ratio (11: co-former)**	**Solvent system**	**Crystallisation technique**	**Product**
hexakis(4-fluorophenoxy)cyclo-triphosphazene	63; 41	1:1	THF	Slow evaporation	crystals of **11**
hexakis(4-iodophenoxy)-cyclotriphosphazene	65; 78	1:1	THF	Slow evaporation	none
imidazole	62; 10	1:3	THF	Slow evaporation	crystals of **11**
α-dibromo-*p*-xylene	63; 30	1:3	THF/DCM	Slow evaporation	α-dibromo-*p*-xylene
α-dibromo-*o*-xylene	64; 36	1:3	THF/DCM	Slow evaporation	none
4-bromobenzonitrile	63; 29	1:3	THF/DCM	Slow evaporation	crystals of **11**
cobalt(II)acetate	60; 18	1:2	THF/MeOH	Layered	crystals of **11**
copper(II)acetate	60; 12	1:2	THF/MeOH	Layered	crystals of **11**
3,4-lutidine	61; 14	1:3	THF	Slow evaporation	crystals of **11**
pyridine	62; 17	1:3	THF	Slow evaporation	crystals of **11**
5	68; 39	1:1	THF	Slow evaporation	crystals of **11**
phosphonitrilic chloride trimer	65; 18	1:1	THF	Slow evaporation	crystals of **11**
bromopentafluoroben-zene	54; 18	1:1	Chloroform/ acetonitrile	Vapour diffusion (AcCN)	crystals of **11**
iodopentafluorobenzene	52; 14	1:1	Chloroform/ acetonitrile	Vapour diffusion (AcCN)	crystals of **11**
bromopentafluorobenzene	51; 52	1:4	Chloroform/ acetonitrile	Vapour diffusion (AcCN)	crystals of **11**

Table S16 Summary of crystallisation experiments with **12** in a range of solvents and with a series of potential co-crystal formers.

Co-former	Quantity (12; co-former) /mg	Mole ratio (12: co-former)	Solvent system*	Crystallisation technique	Product
4-iodoaniline	61; 32	1:3	DCM	Slow evaporation	crystals of **12**
acetonitrile	59	excess	DCM/ acetonitrile	Slow evaporation	none
4-bromobenzonitrile	62; 26	1:3	DCM	Slow evaporation	crystals of **12**
1,3-dicyanobenzene	62; 19	1:3	DCM	Slow evaporation	crystals of **12**
2-cyanopyridine	59; 16	1:3	DCM	Slow evaporation	none
3-cyanopyridine	61; 16	1:3	DCM	Slow evaporation	none
4-cyanopyridine	65; 22	1:3	DCM	Slow evaporation	crystals of **12**
4-iodobenzonitrile	64; 31	1:3	DCM	Slow evaporation	none
benzonitrile	63; 16	1:3	DCM	Slow evaporation	crystals of **12**
nitrobenzene	66; 26	1:3	DCM	Slow evaporation	none
o-tolunitrile	65; 21	1:3	DCM	Slow evaporation	none
m-tolunitrile	61; 22	1:3	DCM	Slow evaporation	none
p-tolunitrile	61; 19	1:3	DCM	Slow evaporation	none
iodophenol	60; 32	1:3	DCM/THF	Slow evaporation	crystals of **12**
1,2-bis(2-pyridyl)ethylene	65; 25	1:3	DCM/THF	Slow evaporation	crystals of **12**
4,4'-diiodobiphenyl	67; 51	1:3	DCM	Slow evaporation	none
1,4-diiodobenzene	64; 46	1:3	DCM	Slow evaporation	none
2-iodopropane	62; 24	1:3	DCM	Slow evaporation	none
propionitrile	64; 13	1:3	DCM	Slow evaporation	none
terephthalonitrile	64; 19	1:3	DCM/ acetonitrile	Slow evaporation	crystals of **12**
4-(4-fluorophenyl)benzonitrile	62; 26	1:3	DCM	Slow evaporation	none
hexakis(4-fluorophenoxy)cyclotri-phosphazene	66; 38	1:1	Chloroform	Slow evaporation	crystals of **12** and **9**
iodopentafluorobenzene	51; 11	1:1	Chloroform/ acetonitrile	Vapour diffusion (AcCN)	crystals of **12**
iodopentafluorobenzene	51; 50	1:4	Chloroform/ acetonitrile	Vapour diffusion (AcCN)	crystals of **12**
bromopentafluorobenzene	50; 24	1:1	Chloroform/ acetonitrile	Vapour diffusion (AcCN)	crystals of **12**

*These crystallisations were also repeated in chloroform

Table S17 Crystallisations from the melt with **9**, **10**, **11** and **12** in a 1:1 mole ratio

Compound 1	**Compound 2**	**Amount (cmp 1; cmp 2) /mg**	**Method**
hexakis(4-fluorophenoxy)-cyclotriphosphazene	hexakis(4-chlorophenoxy)-cyclotriphosphazene	46; 52	Ground together & melted
hexakis(4-fluorophenoxy)-cyclotriphosphazene	hexakis(4-bromophenoxy)-cyclotriphosphazene	45; 68	Ground together & melted
hexakis(4-fluorophenoxy)-cyclotriphosphazene	hexakis(4-iodophenoxy)-cyclotriphosphazene	42; 82	Ground together & melted
hexakis(4-chlorophenoxy)-cyclotriphosphazene	hexakis(4-bromophenoxy)-cyclotriphosphazene	39; 53	Ground together & melted
hexakis(4-chlorophenoxy)-cyclotriphosphazene	hexakis(4-iodophenoxy)-cyclotriphosphazene	41; 66	Ground together & melted
hexakis(4-iodophenoxy)-cyclotriphosphazene	hexakis(4-bromophenoxy)-cyclotriphosphazen	51; 41	Ground together & melted

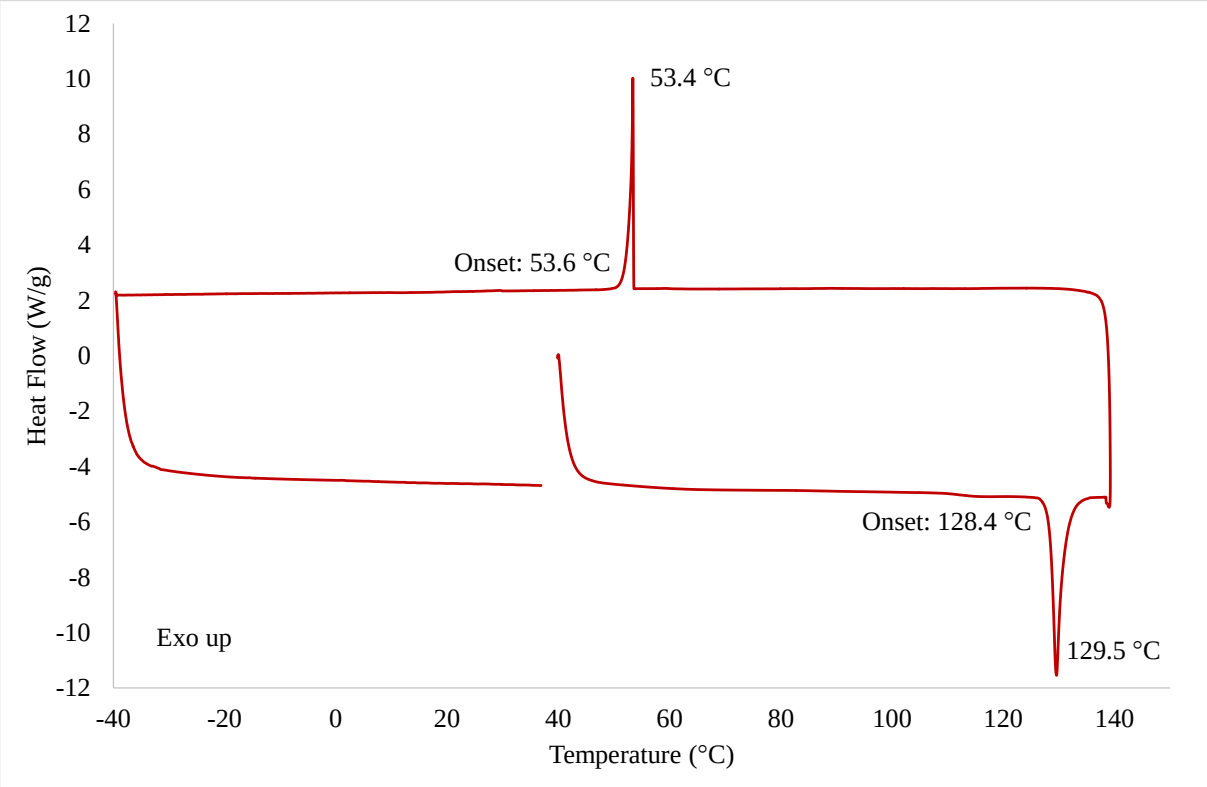


Figure S6 DSC analysis of the monoclinic form of hexakis(4-fluorophenoxy)cyclotriphosphazene (**9**), with a melt at 128.4 °C and a recrystallization event upon cooling at 53.6 °C. This structure undergoes single-crystal to single-crystal polymorphic transitions where **9α** (the monoclinic *P* form) converts to **9γ** between 115 and 125 °C before melting.

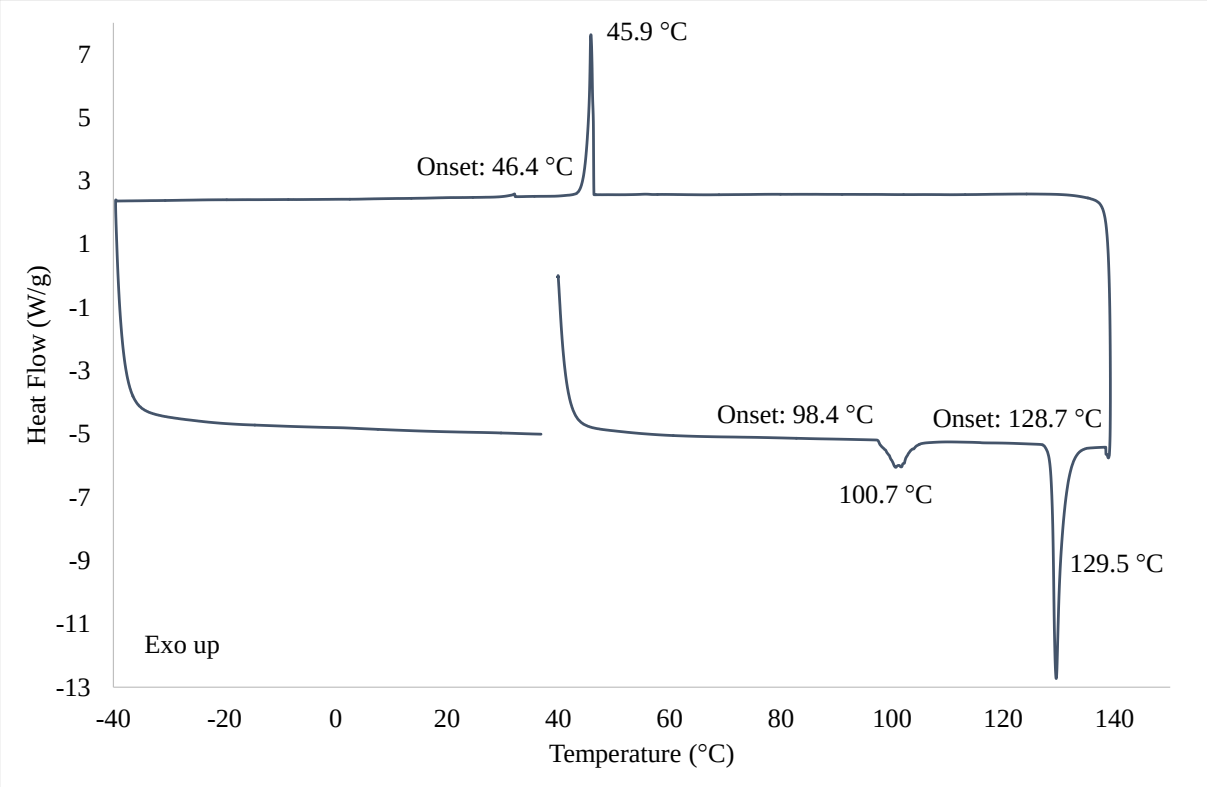


Figure S7 DSC analysis of the triclinic form of hexakis(4-fluorphenoxy)cyclotriphosphazene (**9**). The triclinic form (**9β**) converts to **9γ** around 100 °C before the melt at 129.5 °C.

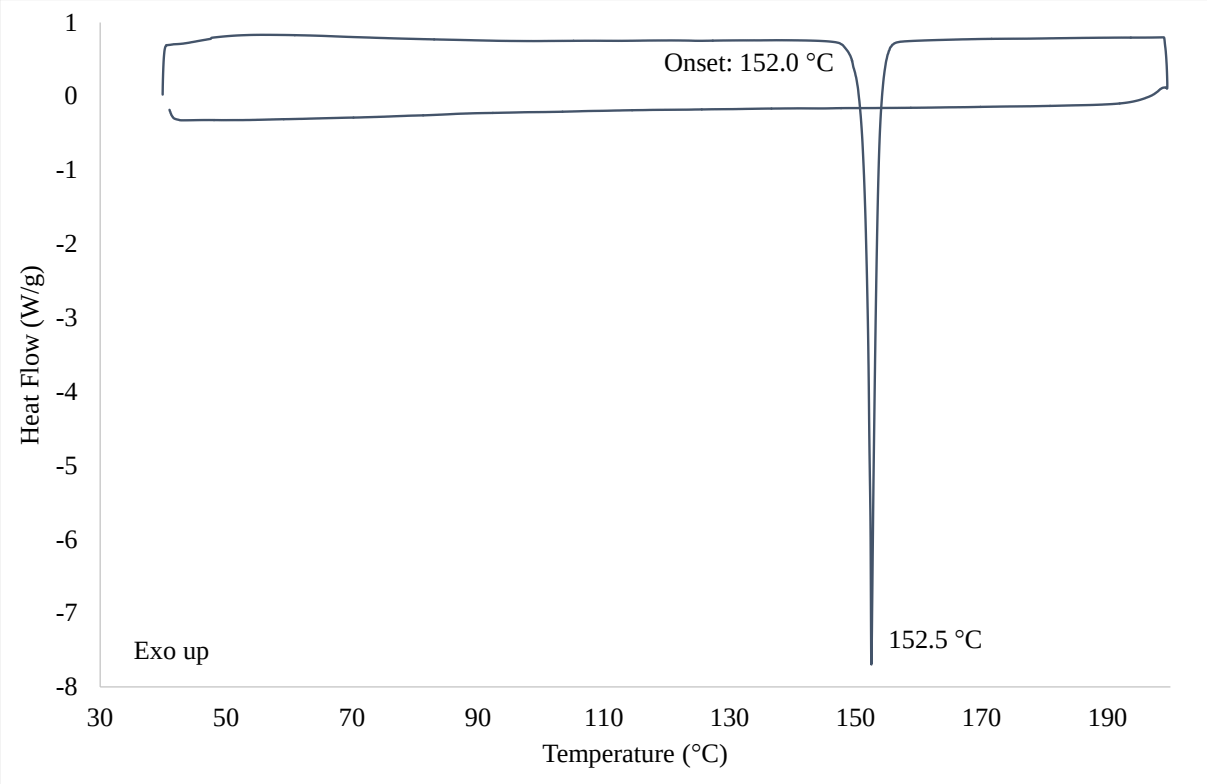


Figure S8 DSC analysis of hexakis(4-chlorophenyl)cyclotriphosphazene (**10**), with a melt occurring at 152.0 °C.

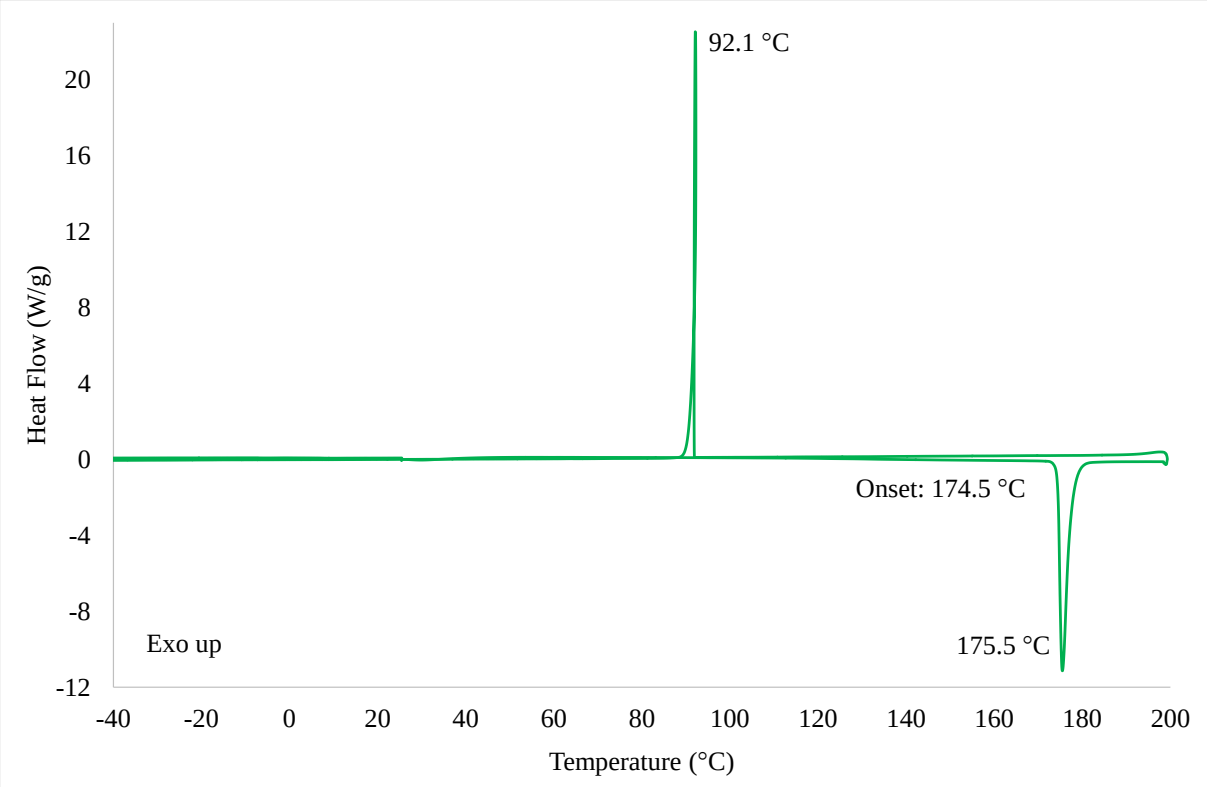


Figure S9 DSC analysis of hexakis(4-bromophenyl)cyclotriphosphazene (**11**), with a melt occurring at 174.5 °C and a recrystallization event upon cooling at 92.1 °C.

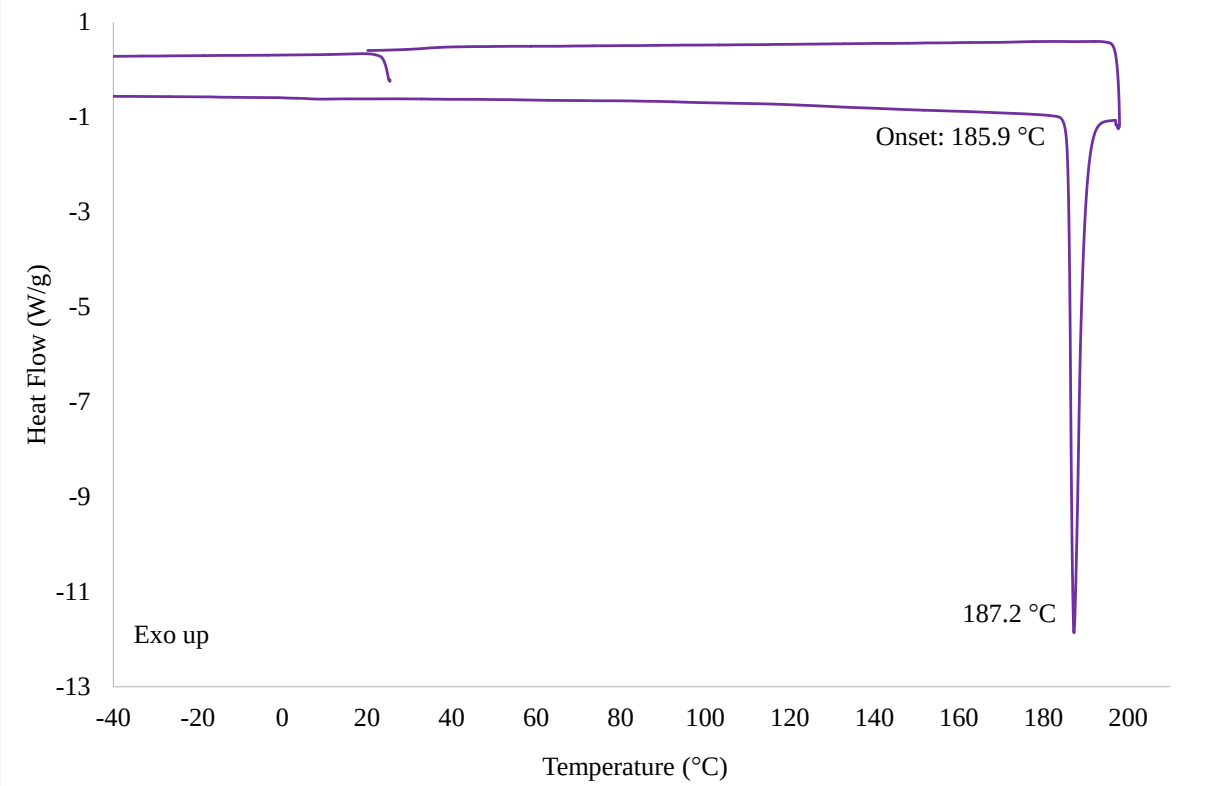


Figure S10 DSC analysis of hexakis(4-iodophenyl)cyclotriphosphazene (**12**), with a melt at 185.9 °C.

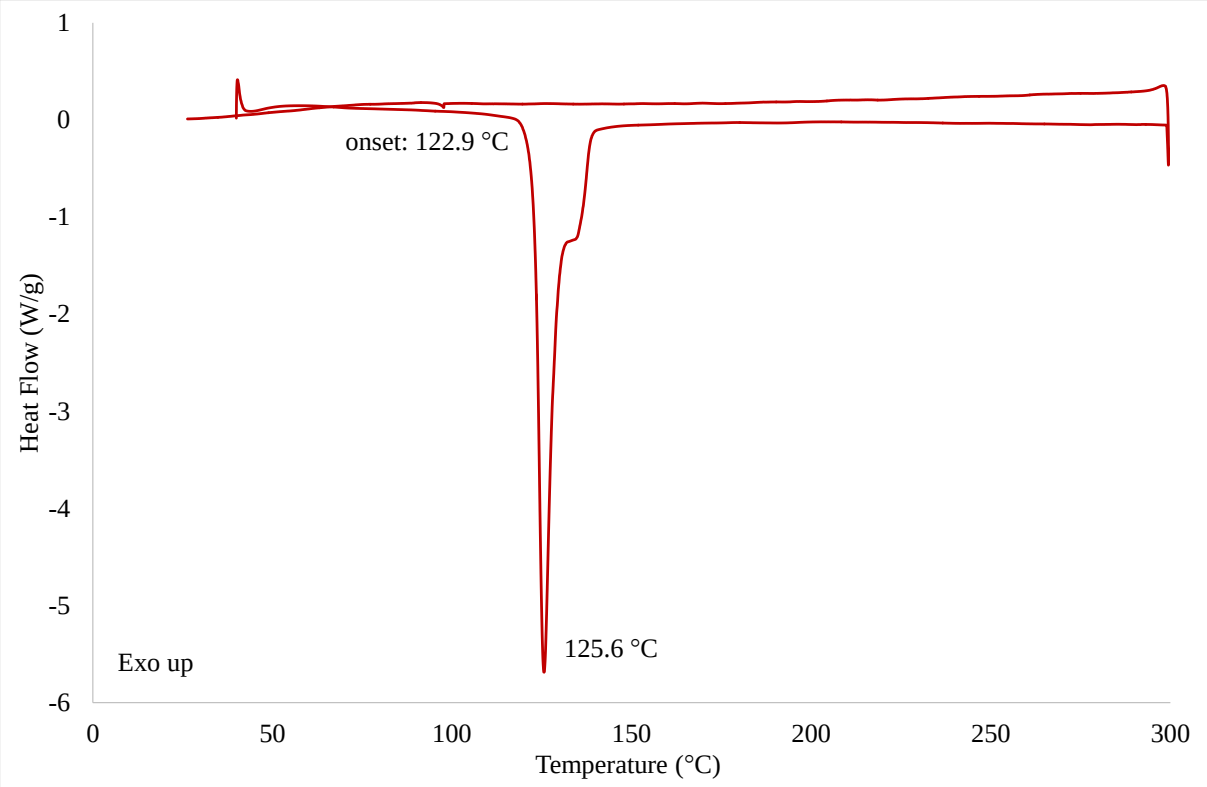


Figure S11 DSC analysis of the melt product (**9/10**) of the fluoro and chloro derivatives. Melting occurs before the melting point of the fluorophenoxy derivative (129 °C).

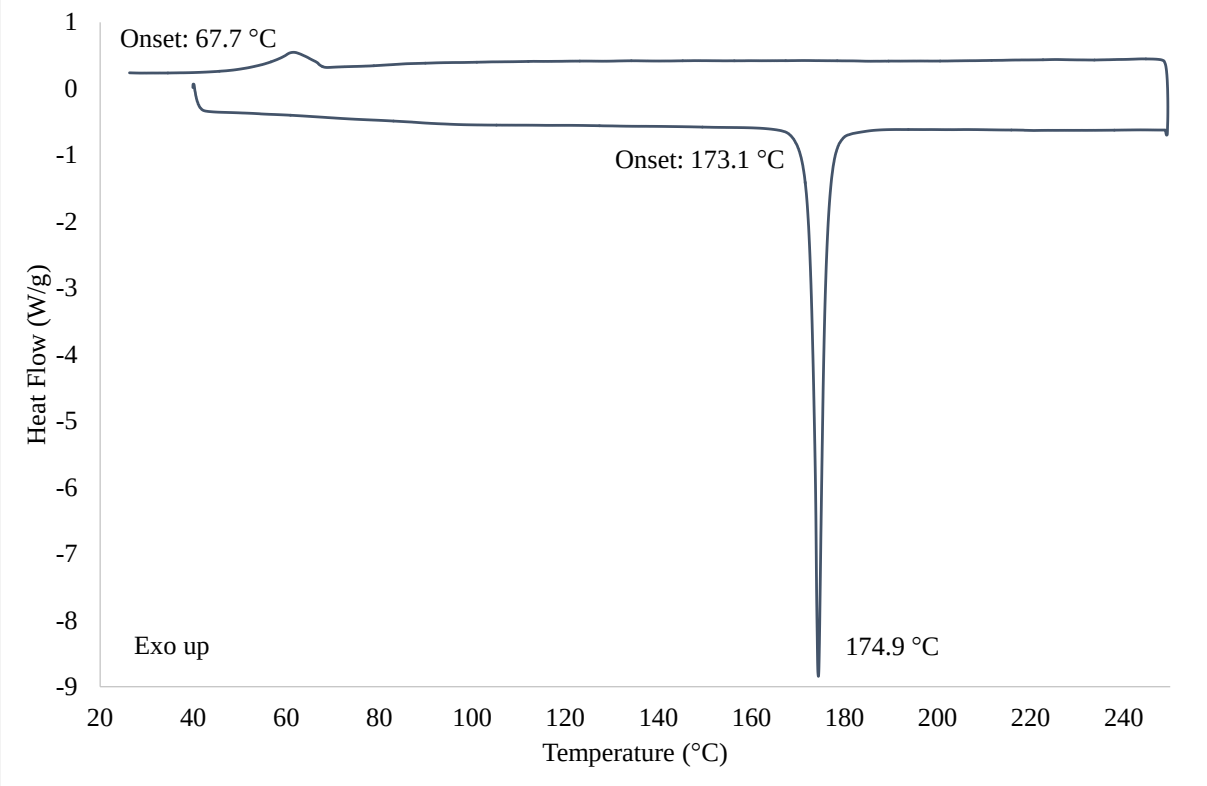


Figure S12 DSC analysis of the product of **11** and **12**. The melting point of **11**/**12** is lower than that of both the reagents.

Synthesis of 1-12

All chemicals were purchased from Sigma-Aldrich and used without further purification. THF, diethylether and toluene were distilled over sodium sand or wire with benzophenone as indicator, under an atmosphere of dry nitrogen. DCM and acetonitrile were distilled over dried calcium hydride under an atmosphere of dry nitrogen. Acetone and *n*-hexane were distilled over dried calcium chloride under nitrogen.

^{1}H and ^{31}P NMR spectra were obtained using a 300 MHz Varian VNMRS or a 400 MHz Varian Unity Inova. Chemical shift values are in ppm and were referenced to either chloroform-*d* or DMSO-d_6. Data for ^{1}H spectra are reported as chemical shift (δ ppm) (integration, multiplicity, coupling constant (Hz)). H_3PO_4 was used as an external standard for ^{31}P NMR.

All reactions were performed under an atmosphere of dry nitrogen unless otherwise stated.

Tris(1,3-diaminopropane)cyclotriphosphazene (1)[1]

$N_3P_3Cl_6$ (0.5 g,1.44 mmol) was dissolved in 50 ml of a 7:3 mixture of *n*-hexane:DCM. To this mixture, 0.8 ml (8.64 mmol) 1,3-diaminopropane was added. The reaction mixture was refluxed for 4 hours, after which the solution was cooled and filtered and the solvent removed under reduced pressure. The resultant white powder was further purified by recrystallisation from methanol. Yield: 62% (0.313 g, 0.89 mmol).

^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 1.53 (2H, m), 3.04 (4H, m), 3.48 (2H, s), ^{31}P NMR (DMSO-d_6, 400 MHz, H_3PO_4): δ ppm 13.86 (d), 20.45 (t).

Crystals of **1** were also grown from a THF/hexane solution. This proved to be the known hydrate.[1a]

4,4,6,6-Tetrachloro-2,2-(biphenyl-2,2'-dioxy)cyclotriphosphazene (2)[2]

A mixture of $N_3P_3Cl_6$ (1.018 g, 2.88 mmol), 2,2'-biphenol (0.543 g, 2.88 mmol) and K_2CO_3 (2.013 g, 14.4 mmol) were stirred together in 40 ml acetone at room temperature for 30 minutes. The volatiles were evaporated *in vacuo* and the residue extracted with 4 x 15 ml DCM. The solvent was evaporated to give a white solid, which was recrystallised from DCM/petroleum ether. Yield: 80% (1.071 g, 2.32 mmol). Mp.: 181 – 189 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.57 (2H, d, *J* = 7.62 Hz), 7.49 (2H, t, *J* = 7.42 Hz), 7.41 (2H, t, *J* = 7.62 Hz), 7.33 (2H, d, 8.01 Hz), ^{31}P NMR ($CDCl_3$, 400 MHz, H_3PO_4): δ ppm 21.87 (d, Cl_2), 9.74 (t, $C_{12}O_2H_8$).

2,2-Dichloro-4,4,6,6-bis[spiro(2',2''-dioxy-1',1''-biphenylyl]cyclotriphosphazene (3)[3]

$N_3P_3Cl_6$ (2 g, 5.75 mmol), biphenyl-2,2'-diol (2.14 g, 11.51 mmol) and K_2CO_3 (3.98 g, 28.77 mmol) were mixed in 20 ml acetone at 0 °C. The reaction mixture was stirred at room temperature for 24 hours, and then the solvent was removed *in vacuo*. The product was extracted by washing with 15 ml of DCM four times, filtering each time with a cannula filter. The solvent was then removed under vacuum, yielding a white powder. Yield: 86% (2.847 g, 4.96 mmol). Mp.: 268 – 275 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 7.55 (4H, d, *J* = 7.63 Hz), 7.46 (4H, d, *J* = 7.63 Hz), 7.36 (8H, m), ^{31}P NMR ($CDCl_3$, 300 MHz, H_3PO_4): δ ppm 19.79 (d, $C_{12}O_2H_8$), 29.19 (dd, Cl_2).

Tris(2,2'-dioxybiphenyl)cyclotriphosphazene (4)[4]

$N_3P_3Cl_6$ (1.003 g, 2.88 mmol), 2,2'-biphenol (1.815 g, 9.66 mmol) and K_2CO_3 (3.010 g, 21.8 mmol) were refluxed for 7 hours in 140 ml acetone. The solvent was evaporated *in vacuo* and the residue washed with 100 ml water, 100 ml aqueous NaOH (0.5 M), 2 x 50 ml water, 50 ml ethanol and 50 ml ether. The white product was dried under vacuum. Yield: 75% (1.278 g, 1.86 mmol). Mp.: >350 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.52 (2H, d, J = 7.62 Hz), 7.41 (4H, m), 7.33 (2H, t, J = 7.642 Hz), ^{31}P NMR ($CDCl_3$, 400 MHz, H_3PO_4): δ ppm 26.27 (s).

2,2-Bis(4-formylphenoxy)-4,4,6,6-bis[spiro(2',2''-dioxy-1',1''-biphenylyl]cyclotriphosphazene (5)[3]

Compound **3** (2 g, 3.48 mmol), 4-hydroxybenzaldehyde (0.854 g, 6.96 mmol) and K_2CO_3 (2.663 g, 19.28 mmol) were added to 20 ml THF at 0 °C. The mixture was refluxed for 5 hours and the solvent removed under vacuum. The resulting solid was extracted with DCM (4 x 10 ml), and the solvent subsequently removed under vacuum. The product was recrystallised from acetone. Yield: 72% (1.881 g, 2.52 mmol). Mp.: 220 – 224 °C

^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 7.07 (2H, d, J = 7.80 Hz), 7.31 – 7.41 (4H, m), 7.54 (4H, t, J = 8.58 Hz), 7.96 (2H, d, 8.19 Hz), 10.01 (1H, s) ^{31}P NMR ($CDCl_3$, 300 MHz, H_3PO_4): δ ppm 9.62 – 11.69 (tt), 25.59 – 26.71 (dt).

Hexakis(4-cyanophenoxy)cyclotriphosphazene (6)[5]

A mixture of 4-cyanophenol (2.071 g, 17.28 mmol) and K_2CO_3 (4.804 g, 34.56 mmol) was prepared in 80 ml THF. $N_3P_3Cl_6$ (1.030 g, 2.88 mmol) in 15 ml THF was added dropwise to this mixture. The reaction mixture was refluxed for 6 hours with vigorous stirring. The solvent was removed *in vacuo* and the residue dispersed in 100 ml water. The resultant white solid was separated by filtration and allowed to dry. Yield: 94 % (2.284 g, 2.707 mmol). Mp.: 263 – 265 °C.

^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 7.16 (2H, d, 8.79 Hz), 7.82 (2H, d, 8.79 Hz), ^{31}P NMR (DMSO-d_6, 400 MHz, H_3PO_4): δ ppm 8.51 (s).

Hexakis(4-pyridyloxy)cyclotriphosphazene (7)[6]

4-hydroxypyridine (0.826 g, 8.64 mmol) and K_2CO_3 (1.818 g, 12.96 mmol) were added to 50 ml THF. $N_3P_3Cl_6$ (0.503 g, 1.44 mmol) was added to this mixture, which was then stirred for two and a half days at room temperature, after which it was refluxed for approximately 6 hours. The solvent was removed under vacuum and the residue washed with 100 ml water. The product was isolated by filtration and dried *in vacuo* to yield a light yellow product. Yield: 89% (0.897 g, 1.28 mmol). Mp.: 163 – 165 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 6.93 (2H, d, 6.44 Hz), 8.50 (2H, d, 6.25 Hz), ^{31}P NMR ($CDCl_3$, 400 MHz, H_3PO_4): δ ppm 7.30 (s).

Hexakis(4-hydroxyphenoxy)cyclotriphosphazene (8)[7]

Hexakis(4-methoxyphenoxy)cyclotriphosphazene

A suspension of sodium 4-methoxyphenoxide was prepared in 20 ml dry THF by allowing 4-methoxyphenol (4.274 g, 34.5 mmol) to react with NaH (1.385 g as a 60 % dispersion in mineral oil; equivalent to 0.828 g, 34.5 mmol pure NaH). The NaH was washed with dry petroleum ether to remove the mineral oil prior to use. A solution of $N_3P_3Cl_6$ (2 g, 5.75 mmol) in 20 ml THF was added dropwise to this suspension. On complete addition of the phosphonitrilic chloride trimer, the reaction mixture was refluxed for 24 hours with stirring. The reaction mixture was cooled and washed with 100 ml water in order to precipitate the product as a white powder. Yield: 82% (4.136 g, 4.733 mmol). Mp.: 105 – 106 °C

^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 3.72 (3H, s), 6.77 (4H, s)

Hexakis(4-hydroxyphenoxy)cyclotriphosphazene (**8**)

Hexakis(4-methoxyphenoxy)-cyclotriphosphazene (3 g, 3.43 mmol) was dissolved in 30 ml DCM. A solution of BBr_3 (2 ml, 20.6 mmol) in 30 ml DCM was added dropwise to the solution of cyclotriphosphazene. The solution was allowed to stir for 3 hours, after which it was poured carefully into 100 ml of water to precipitate the product. The white precipitate was filtered off, washed with water and dried. Yield: 85% (2.303 g, 2.92 mmol).

^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 6.59 (2H, s), 6.61 (2H, s), ^{31}P NMR (DMSO-d_6, 400 MHz, H_3PO_4): δ ppm 22.32 (s).

Hexakis(4-fluorophenyl)cyclotriphosphazene (9)[8,9]

This synthetic procedure was not performed under inert conditions.

4-fluorophenol (1.94 g, 17.28 mmol) and $N_3P_3Cl_6$ (0.998 g, 2.88 mmol) were dissolved in 60 ml acetone. K_2CO_3 (4.797 g, 120.96 mmol) was added to this mixture, and the reaction mixture was refluxed for 12 hours. The precipitate was filtered off, washed with DCM and combined with the filtrate. The solvent was then removed *in vacuo*. The white powder thus obtained was recrystallised from methanol. Yield: 65% (3.131 g, 3.91 mmol). Mp. 129 °C

^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 6.88 (2H, s), 6.9 (2H, s), ^{31}P NMR ($CDCl_3$, 400 MHz, H_3PO_4): δ ppm 9.86 (s).

Hexakis(4-chlorophenyl)cyclotriphosphazene (10)[8]

4-chlorophenol (2.240 g, 17.28 mmol) and K_2CO_3 (4.793 g, 34.56 mmol) were stirred together in 50 ml acetone. $N_3P_3Cl_6$ (1.004 g, 2.88 mmol) dissolved in 10 ml acetone was added to the mixture, which was then refluxed for 1 day. The solvent was removed under vacuum and the product extracted with DCM. The product was further purified by recrystallisation from acetonitrile. Yield: 76 % (1.982 g, 2.2 mmol). Mp. 152 °C

^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 6.68 (2H, d, 8.20 Hz), 7.17 (2H, d, 8.40 Hz), ^{31}P NMR ($CDCl_3$, 400 MHz, H_3PO_4): δ ppm 9.59 (s).

Hexakis(4-bromophenyl)cyclotriphosphazene (11)[8]

4-bromophenol (3.030 g, 17.28 mmol) and K_2CO_3 (4.779 g, 34.56 mmol) were added to 50 ml acetone. $N_3P_3Cl_6$ (1.011 g, 2.88 mmol) in 10 ml acetone was added to the mixture, which was then refluxed for 2 days. The solvent was removed under vacuum and the product purified by recrystallisation from acetonitrile. Yield: 79 % (2.684 g, 2.3 mmol). Mp. 176.8 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 6.75 (2H, d, 8.79 Hz), 7.33 (2H, d, 8.89 Hz), ^{31}P NMR ($CDCl_3$, 400 MHz, H_3PO_4): δ ppm 9.29 (s).

Hexakis(4-iodophenyl)cyclotriphosphazene (12)[8]

4-iodophenol (3.844 g, 17.28 mmol) and $N_3P_3Cl_6$ (1.007 g, 2.88 mmol) were dissolved in 75 ml acetone. K_2CO_3 (4.821 g, 34.56 mmol) was added to this mixture, which was refluxed for 2 days. The solvent was evaporated under vacuum and the product was extracted with 3 x 20 ml DCM. The product was further purified by recrystallisation from acetonitrile. Yield: 65% (2.702 g, 1.86 mmol). Mp. 187.6 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 6.62 (2H, d, J = 8.79 Hz), 7.52 (2H, d, 8.79 Hz), ^{31}P NMR ($CDCl_3$, 400 MHz, H_3PO_4): δ ppm 9.27 (s).

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