Isomer-Dependent Cytostatic Activity of Bis(1-aziridinyl)cyclophosphazenes

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A number of recently synthesized mono- and bis(1-aziridinyl) derivatives of the inorganic ring systems $(NPCl_2)_3$ and $(NPCl_2)_4$ was tested for their cytostatic activity in vitro (L1210 and L5178Y cells) and in vivo (intraperitoneal leukemia L1210 in CDF_1 mice). Generally, the nongeminal bis(1-aziridinyl) isomers (either trans or cis) appear to be potent tumor growth inhibitors in contrast to their geminally substituted and mono(1-aziridinyl)-substituted analogues. A relationship between the biological activity and the number of alkylating centers (i.e., P atoms carrying one or two aziridinyl groups) is proposed.

The use of cyclophosphazenes or cyclophosphathiazenes as carrier molecules for aziridinyl groups is known to afford powerful cytostatic agents.[1-11] Three derivatives with trade names Apholate (1,1,3,3,5,5-hexakis(1-aziridinyl-2,4,6,1λ⁵,3λ⁵,5λ⁵-triazatriphosphorine), Fotrin (1,1,3,3,5-pentakis(1-aziridinyl)-5-morpholino-2,4,5,1λ⁵,3λ⁵,5λ⁵-triazatriphosphorine), and SOAz (1,3,3,5,5-pentakis(1-aziridinyl)-1λ⁶,2,4,6,3λ⁵,5λ⁵-thiatriazadiphosphorine 1-oxide) have received considerable attention. Both Fotrin (USSR) and SOAz (The Netherlands, France) have been studied in clinical trials.[3-5,12-17] SOAz, administered intravenously, was remarkably well tolerated by most patients. At high dose levels delayed bone marrow toxicity occurred, which appeared dose limiting. Although this myelosuppression is a commonly encountered phenomenon on cytostatic aziridinyl derivatives (e.g., TEM and Thiotepa) further clinical trials had to be cancelled because of the cumulative tendency of this toxicity.[14-17]

In a previous paper,[10] we emphasized the effect of substituents R on the in vitro cytostatic activity of a series of derivatives of the six-membered ring system $(NPCl_2)_3$ (1) with formula $N_3P_3Az_nR_{6-n}$ (Az = 1-aziridinyl (NC_2H_4); n = 3–6). The simultaneous determination of the 50% inhibition dose (ID_{50}) in L1210 mouse leukemia cells and of the lowest active dose (LAD) in L5178Y mouse lymphoma cells led to the conclusion that the presence of electron-donating substituents attached to the N-P ring system is essential for effective tumor growth inhibition. Hydrolytic instability appeared to give loss of activity.

In the same study the biological activity of the compounds concerned was suggested to depend on the number of alkylating centers (i.e., PAz_2 or PAzR) rather than on the number of aziridinyl groups present in the molecule. As a result of our investigations to the aziridinolysis patterns of the homologues $(NPCl_2)_3$ (1) and $(NPCl_2)_4$ (2),[18-20] starting materials have become available for the synthesis of an additional series of compounds containing only one or two alkylating centers, viz. $N_3P_3AzR_5$, $N_3P_3Az_2R_4$ (three isomers; see Figure 1A), $N_4P_4AzR_7$, and $N_4P_4Az_2R_6$ (five isomers; see Figure 1B).

In this paper the cytostatic activity of amino aziridinyl derivatives (R = NHMe, NMe_2, NC_4H_8, NC_4H_8O) will be discussed in view of the mutual intramolecular positions of the aziridinyl groups. In this respect also, attention will be drawn to N–P ring size and flexibility. All derivatives prepared were tested in previously published in vitro assays[9,10] employing L5178Y and L1210 cells, respectively. Also, in vivo experiments determining the activity of a

Table I. Cytostatic Activity in Vitro of Compounds $N_3P_3AzR_5$ and $N_3P_3Az_2R_4$ (R = NHMe, NMe_2, Pyr,[a] Morph[b])

compound	L1210: ID_{50}, 10^{-6} mol L^{-1}	L5178Y: LAD, 10^{-6} mol L^{-1}
$N_3P_3Az(NHMe)_5$ (3)	>250	200
gem-$N_3P_3Az_2(NHMe)_4$ (4)	27.8	8
trans-$N_3P_3Az_2(NHMe)_4$ (5)	3.3	1.0
cis-$N_3P_3Az_2(NHMe)_4$ (6)	5.0	1.0
$N_3P_3Az(NMe_2)_5$ (7)	>250	>300
gem-$N_3P_3Az_2(NMe_2)_4$ (8)	19.5	20
trans-$N_3P_3Az_2(NMe_2)_4$ (9)	2.9	0.5
cis-$N_3P_3Az_2(NMe_2)_4$ (10)	7.3	0.5
$N_3P_3Az(Pyr)_5$ (11)	44.3	12
gem-$N_3P_3Az_2(Pyr)_4$ (12)	18.6	4
trans-$N_3P_3Az_2(Pyr)_4$ (13)	4.8	1.0
cis-$N_3P_3Az_2(Pyr)_4$ (14)	6.7	1.0
$N_3P_3Az(Morph)_5$ (15)	>250	>300
gem-$N_3P_3Az_2(Morph)_4$ (16)	130	120
trans-$N_3P_3Az_2(Morph)_4$ (17)	24.7	30
cis-$N_3P_3Az_2(Morph)_4$ (18)	33.5	60

[a] Pyr = 1-pyrrolidinyl ($-NC_4H_8$). [b] Morph = morpholino ($-NC_4H_8O$).

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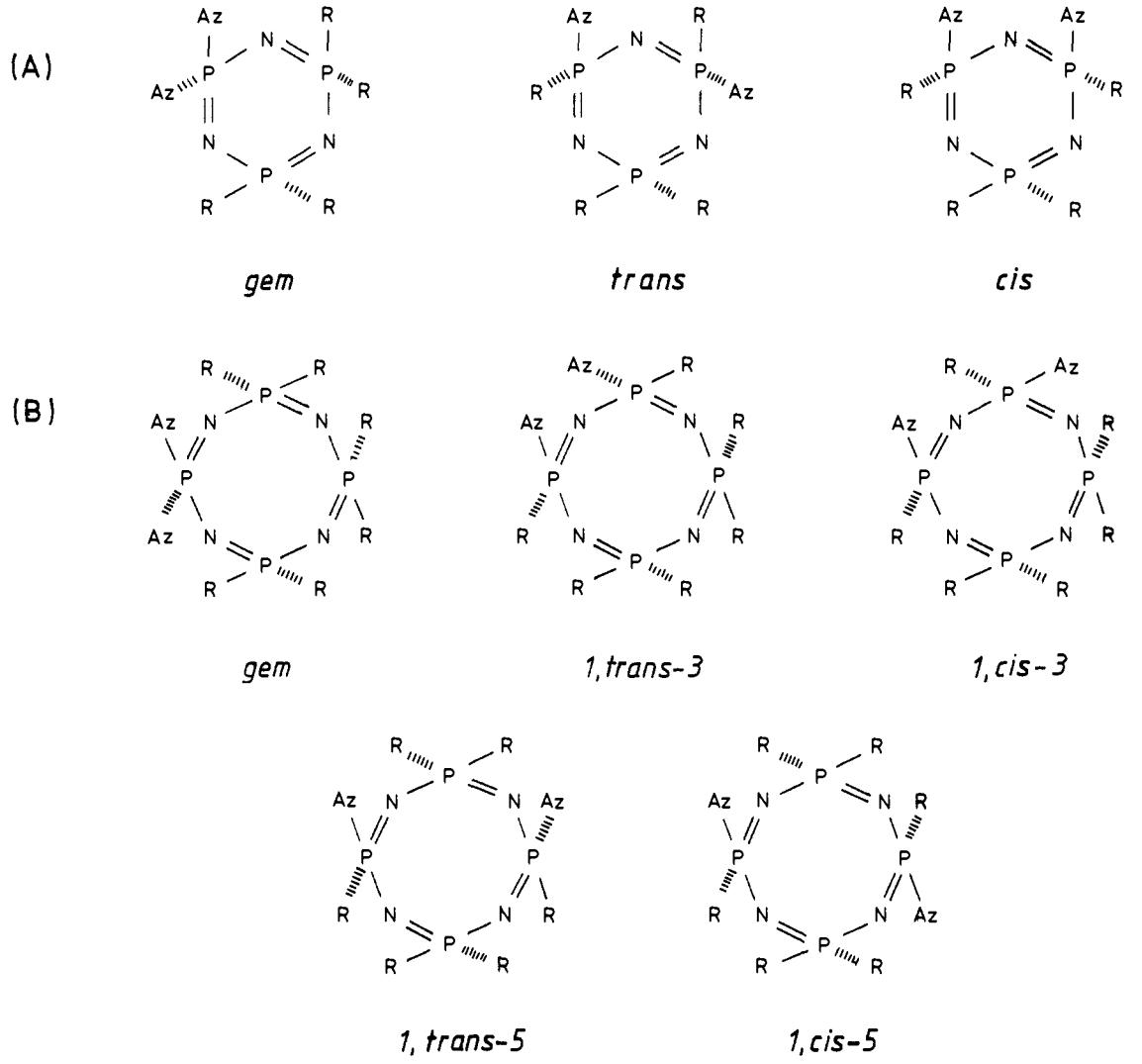

Figure 1. Representations of the isomers $N_3P_3Az_2R_4$ (A) and $N_4P_4Az_2R_6$ (B).

selection of these compounds against leukemia L1210 in mice will be discussed.

Results and Discussion

In Vitro Studies. In Table I the ID_{50} and LAD values of the isomeric bis(aziridinyl) and the mono(aziridinyl) derivatives of **1** are listed. Although a direct comparison of the ID_{50} and LAD values is hardly feasible, the same trends can be observed within both series. Obviously, the nongeminal bis(aziridinyl) isomers appear to have a systematically higher activity than their geminal analogues, whereas in all cases a dramatic decrease of the activity is observed for the mono(aziridinyl) derivatives. On the basis of these findings and those obtained in the same test systems for tetrakis(aziridinyl) diamino derivatives of **1**[10] (ID_{50} = (1.6–5.8) × 10^{-6} M; LAD = (1.0–4) × 10^{-6} M) it can be argued that at least two alkylating centers (i.e., PAz_2 or PAzR) are required for effective tumor growth inhibition. Probably, this can be associated with the occurrence of cross-linking in the biological tissues.

Regarding the ID_{50} values of the isomeric derivatives in Table I, a general sequence in activity is found: *gem* << cis ≤ trans. It is well-known that the distance between alkylating groups can affect the activity of a cytostatic agent.[21] The compounds with a nongeminal structure

Table II. Cytostatic Activity in Vitro of Some Geminal Bis(aziridinyl) Derivatives

compound	L1210: ID_{50}, 10^{-6} mol L^{-1}	L5178Y: LAD, 10^{-6} mol L^{-1}
gem-$N_3P_3Az_2Cl_4$ (**19**)	34.0	22
$N_3P_3Az_2Pyr_2Cl_2$[a] (**20**)	13.6	250
gem-$N_3P_3Az_2(NH_2)_2Cl_2$ (**21**)	3.2	0.25
gem-$N_3P_3Az_2(NH_2)_2(NHMe)_2$ (**22**)	50.5	8

[a] 1,1-Bis(1-aziridinyl)-*cis*-3,5-dichloro-3,5-bis(1-pyrrolidinyl) derivative.

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Table III. Cytostatic Activity in Vitro of Compounds $N_4P_4AzR_7$ and $N_4P_4Az_2R_6$ (R = NHMe, NMe_2)[a]

compound	L1210: ID_{50}, 10^{-6} mol L^{-1}	L5178Y: LAD, 10^{-6} mol L^{-1}
$N_4P_4Az(NHMe)_7$ (23)	56.9	150
gem-$N_4P_4Az_2(NHMe)_6$ (24)	6.5	18
1,*trans*-3-$N_4P_4Az_2(NHMe)_6$ (25)	1.8	2
1,*trans*-5-$N_4P_4Az_2(NHMe)_6$ (27)	4.6	0.5
1,*cis*-5-$N_4P_4Az_2(NHMe)_6$ (28)	4.6	0.5
$N_4P_4Az(NMe_2)_7$ (29)	12.1	64
gem-$N_4P_4Az_2(NMe_2)_6$ (30)	11.9	2
1,*trans*-3-$N_4P_4Az_2(NMe_2)_6$ (31)	6.6	2
1,*trans*-5-$N_4P_4Az_2(NMe_2)_6$ (33)	7.5	1.0
1,*cis*-5-$N_4P_4Az_2(NMe_2)_6$ (34)	5.5	4

[a] Attempts to purify the 1,cis-3 isomers 26 and 32 were unsuccessful (see the Experimental Section).

might be more versatile in the event of a cross-linking reaction than their geminal isomers.

The size of the amino substituents might as well affect the ultimate cytostatic activity; the derivatives of the relatively smaller amines (i.e., methylamine and dimethylamine) tend to be more active than those of the more bulky ones (i.e., pyrrolidine and morpholine). In their turn the morpholino derivatives are deactivated compared with other ones, in line with the lower electron-releasing capacity of the morpholino substituents (cf. ref 10).

In Table II the activities in vitro of some additional geminal bis(aziridinyl) derivatives are listed. Whereas most of these compounds show lower activities, like the geminal derivatives in Table I, *gem*-$N_3P_3Az_2(NH_2)_2Cl_2$ (21) appears to be a strongly cytostatic agent. This is rather exceptional as, for example, it concerns a chloro derivative, which generally predicts a poor activity (cf. 19 and 20). The decrease in activity on replacing the chloro ligands by methylamino groups leading to compound 22 is also unexpected in view of the resulting increase of electron density on the N–P ring system. In contradiction with other chloro derivatives, 21 is highly soluble in water and, once dissolved, shows a remarkable stability. Although the latter property might partly explain the cytostatic effectiveness of this agent, it is possible that synergetic effects are involved, like intramolecular hydrogen bridge formation between NH_2 and Az groupings, thereby activating the three-membered rings.

The cytostatic activities of the tetrameric mono- and bis(aziridinyl) derivatives (Table III) show approximately the same trends as observed for the trimeric analogues (cf. Table I). Generally, the mono(aziridinyl) and the geminal bis(aziridinyl) derivatives have lower activities than the nongeminal bis(aziridinyl) derivatives, irrespective of the cis or trans structure of the latter compounds. It appears that the ID_{50} and LAD values of the corresponding nongeminal trimeric and tetrameric derivatives are of the same order (cf. Tables I and III), indicating that a comparable cytostatic activity can be attained for both ring systems.

Apart from these similarities the comparison of the data in Tables I and III also touches on some differences. The variations in activity within the series $N_4P_4Az_2(NHMe)_6$ (24–28) and $N_4P_4Az_2(NMe_2)_6$ (30–34) are less pronounced than in the analogous trimeric series (i.e., 4–6 and 8–10 in Table I). This observation might be explained by the higher flexibility of the eight-membered N–P ring system, leveling the structural differences between the various isomers.

In Vivo Studies. The antitumor activity on intraperitoneal leukemia L1210 in CDF_1 mice was determined for a selection of compounds 3–34 and of those described in ref 10. The main selection criteria were accessibility, water solubility, and, in the majority of cases, ID_{50} values below 10^{-5} M. The T/C values, attained with single doses of the compounds, are listed in Table IV together with the activities on L1210 measured in vitro.

Most of the compounds are significantly active in vivo (T/C > 125%), except 33 and the ethylglycinato derivative *gem*-$N_3P_3Az_4(GlyE)_2$. For the latter derivative this is probably caused by its hydrolytic instability.[10] At optimum doses the other compounds $N_3P_3Az_nR_{6-n}$ (n = 4–6) show moderately high T/C values ranging from 163 to 213%. Whereas the low effectivity in vitro of 3, 4, and 17 nicely agrees with their in vivo behavior, the nongeminal methylamino derivatives (5, 6, 25–28) all show excellent T/C values often accompanied by long-term survivors. On the basis of these results this new class of "two-center" agents can be considered as very promising. Apparently, the 1,3-substituted compounds require lower doses and have lower LD_{50} values than the 1,5-substituted analogues. However, these compounds have similar T/C values.

The relatively high water solubility of these methylamino derivatives might be an important propagating factor for their activity against L1210 leukemia. In studies on the activity of 2,5-bis(1-aziridinyl)-*p*-benzoquinones against L1210 Leukemia,[22,23] the more hydrophilic compounds were also shown to be most effective. Notwithstanding possible mechanistic differences between this class of compounds and the aziridinylcyclophosphazenes, this might be an explanation for the low efficacy of the relatively badly water-soluble compounds, viz. 33 and *gem*-/*trans*-$N_3P_3Az_4Pip_2$.

One of the methylamino derivatives, viz. *trans*-$N_3P_3Az_2(NHMe)_4$ (code name AZP; Figure 2), is now under investigation in a phase I clinical trial in the University Hospital of Groningen, The Netherlands. The outcome of this study will be published shortly.

Experimental Section

Screening Methods. The cytostatic activity in vitro on lymphoma L5178Y and leukemia L1210 cells was determined by using previously published methods.[9,10]

Drug effectiveness against leukemia L1210 cells in vivo was determined as described earlier.[24] Briefly, from an in vitro suspension culture, 10^5 leukemia L1210 cells were injected ip into male (BALB/c × DBA/2)F1 mice. After 24 h groups of leukemic mice were treated with different doses of the cyclophosphazene derivatives (five mice per drug dose; 10 mice not treated, used as controls). The survival times of the mice were recorded. End point for drug effectiveness was the prolongation of life span. It is expressed as percent median survival time of drug-treated mice over that of untreated control mice (T/C percent).

Synthesis. All experiments were carried out under dry nitrogen. Purified aziridinylcyclophosphazenes could be stored in a dry atmosphere for prolonged periods without notable changes. Methylamine, dimethylamine, pyrrolidine, and morpholine were distilled prior to use over KOH pellets. Solvents were purified and dried according to conventional methods. The precursors $N_3P_3AzCl_5$, *gem*-, *trans*-, and *cis*-$N_3P_3Az_2Cl_4$, $N_4P_4AzCl_7$, and *gem*-, 1,*trans*-3-, 1,*cis*-3-, 1,*trans*-5-, and 1,*cis*-5-$N_4P_4Az_2Cl_6$ were prepared as described elsewhere.[19,20]

Melting points (uncorrected) were determined on a Buchi melting point apparatus. Elemental analyses were carried out under the supervision of A. F. Hamminga (Microanalytical De-

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Table IV. Cytostatic Activity in Vitro and in Vivo on Leukemia L1210

compound	ID_{50}, 10^{-6} mol L^{-1}	LD_{50},[a] mg kg^{-1}	dose, mg kg^{-1}	T/C,[b] %	LTS[c]
$N_3P_3Az(NHMe)_5$ (3)	>250	800–1000	600	175	1
			900	225	
gem-$N_3P_3Az_2(NHMe)_4$ (4)	27.8	600–800	400	163	
			600	150	
			800	188	
trans-$N_3P_3Az_2(NHMe)_4$ (5)	3.3	50–60	30	200	1
			40	222	2
			50	289	1
cis-$N_3P_3Az_2(NHMe)_4$ (6)	5.0	70–80	40	250	1
			60	275	1
			80	175	
trans-$N_3P_3Az_2(Morph)_4$ (17)	24.7	800–1000	600	163	
			900	163	
gem-$N_3P_3Az_2(NH_2)_2Cl_2$ (21)	3.2	60–70	40	178	
			50	211	1
1,*trans*-3-$N_4P_4Az_2(NHMe)_6$ (25)	1.8	100–120	40	238	2
			60	275	
			80	263	
			100	213	
1,*trans*-5-$N_4P_4Az_2(NHMe)_6$ (27)	4.6	200–250	70	289	1
			100	244	2
			140	333	1
			180	311	
1,*cis*-5-$N_4P_4Az_2(NHMe)_6$ (28)	4.6	200–250	150	200	
			200	213	
1,*trans*-5-$N_4P_4Az_2(NMe_2)_6$ (33)	7.5	150–200	120	125	
			160	<100	
gem-$N_3P_3Az_4(Morph)_2$[d]	5.8	400	300	175	
			350	200	
trans-$N_3P_3Az_4(Morph)_2$[d]	4.7	250	160	213	1
			200	200	
gem-$N_3P_3Az_4(Pip)_2$[d,e]	3.6	250	200	156	
			240	167	
trans-$N_3P_3Az_4(Pip)_2$[d,e]	2.1	140	90	167	
			110	189	
gem-$N_3P_3Az_4(Pyr)_2$[d]	2.7	220	160	178	
			200	211	
gem-$N_3P_3Az_4(GlyE)_2$[d,f]	7.2	170	120	125	
			150	<100	
$N_3P_3Az_5(Pip)$[d,e]	1.5	80	60	175	
			70	213	1
$N_3P_3Az_5(NHMe)$[d]	1.2	45	35	188	1
			40	188	
$N_3P_3Az_6$[d]	2.0	50	20	200	
			40	163	
$N_3P_2SOAz_5(SOAz)$[d]	10.6	250	175	188	1
			200	163	

[a] 50% lethal dose. [b] Treated/control. [c] Long-term survivors (60 days) within a group of five mice. [d] Compound described in ref 10. [e] Pip = piperidino ($-NC_5H_{10}$). [f] GlyE = ethylglycinato ($-N(H)CH_2CO_2C_2H_5$).

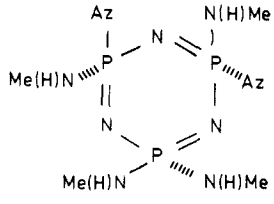

Figure 2. *trans*-$N_3P_3Az_2(NHMe)_4$ (AZP).

partment, University of Groningen). Mass spectra were recorded on an AEI M.S.9 mass spectrometer as a routine purity check (A. Kiewiet, Department of Organic Chemistry, University of Groningen).

$^{13}P\{^1H\}$ NMR spectra were taken from $CDCl_3$ solutions with a Nicolet 283AFT spectrometer in 10-mm tubes at 80.9 MHz; $(NPCl_2)_3$ was used as external reference (=19.9 ppm); the ^2H resonance of the solvent was used for field frequency lock. Most of the trimeric derivatives prepared incorporate two nonequivalent phosphorus nuclei (AB_2 or A_2B type $^{31}P\{^1H\}$ NMR spectra); the three nonequivalent phosphorus nuclei in compounds 21 and 22 lead to ABC type spectra. Tetrameric derivatives are characterized by A_2B_2 (1,5 isomers), AA'BB' (1,3 isomers), or AB_2C type spectra (compounds $N_4P_4AzR_7$ and *gem*-$N_4P_4Az_2R_6$). Combining these data (Table V) with the structures of the precursors[20] led to an unambiguous structure assignment.

$N_3P_3AzR_5$ and $N_3P_3Az_2R_4$ (R = NHMe, NMe_2, Pyr, Morph; 3–18). The preparations were carried out, in either C_6H_6 (R = NHMe, NMe_2, Morph) or Et_2O (R = Pyr). To a stirred solution of one of the precursors $N_3P_3AzCl_5$ or $N_3P_3Az_2Cl_4$ (gem, trans, or cis; 1.4 mmol, 0.5 g) in 15 mL of solvent, cooled at 5 °C, was added dropwise a solution of an excessive amount of the desired amine ($MeNH_2$, 50 mmol; Me_2NH, 35 mmol; C_4H_8NH, 28 mmol; C_4H_8ONH, 42 mmol) in 20 mL of solvent. After warming to room temperature and a reaction time of 18 h, the temperature of the reaction mixture was raised to 50 °C (C_6H_6) or 35 °C (Et_2O) for an additional period (see Table V). Precipitated amine–hydrochloride salt was filtered off, and after thorough washing with solvent the combined filtrates were evaporated in vacuo. The crude product was purified by recrystallization from a suitable solvent or by sublimation (see Table V).

***gem*-$N_3P_3Az_2(NH_2)_2Cl_2$ (21).** A solution of *gem*-$N_3P_3Az_2Cl_4$ (2.3 mmol, 0.8 g) in 30 mL of MeCN, cooled at −10 °C, was saturated with NH_3 for 30 min. Filtration of precipitated NH_4Cl and evaporation of the filtrate yielded a solid, which afforded 0.53 g of 21 upon recrystallization from CH_2Cl_2–Et_2O. Further data are given in Table V.

***gem*-$N_3P_3Az_2(NH_2)_2(NHMe)_2$ (22).** To a stirred solution of 21 (1.55 mmol, 0.5 g) in 20 mL of $CHCl_3$, cooled at 0 °C, was added

Table V. Chemical and Physical Properties of the Mono- and Bis(aziridinyl)cyclophosphazenes Prepared

no.	reactn time, h	recryst solvent[a]	yield, %	mp, °C	formula[b]	^{31}P NMR[c] δ(P)	$^{2}J_{PP}$	$^{4}J_{PP}$
3	24	A	49	154–156	$C_7H_{24}N_9P_3$	30.5, 21.9	40.0	
4	24	A	63	147–148	$C_8H_{24}N_9P_3$	38.2, 21.8	37.9	
5	24	A	73	153–155	$C_8H_{24}N_9P_3$	30.0, 22.1	37.4	
6	48	A	40	152–153	$C_8H_{24}N_9P_3$	29.9, 22.0	38.5	
7	68	*d*	62	54–56	$C_{12}H_{34}N_9P_3$	31.5, 25.9	39.1	
8	48	B	50	85–87.5	$C_{12}H_{32}N_9P_3$	37.7, 25.6	38.4	
9	48	*d*	36	60–63	$C_{12}H_{32}N_9P_3$	31.6, 25.4	37.4	
10	48	*d*	20	60–61	$C_{12}H_{32}N_9P_3$	30.9, 25.6	37.3	
11	30	B	30	106–108	$C_{22}H_{44}N_9P_3$	27.8, 17.3	38.5	
12	20	B	70	97–98	$C_{20}H_{40}N_9P_3$	37.1, 16.9	37.9	
13	20	B	32	93.5–94.5	$C_{20}H_{40}N_9P_3$	27.6, 17.0	37.6	
14	66	B	22	112–116	$C_{20}H_{40}N_9P_3$	27.5, 17.1	37.7	
15	100	C	20	151–154	$C_{22}H_{44}N_9O_5P_3$	27.6, 19.8	39.1	
16	48	C	55	158–159.5	$C_{20}H_{40}N_9O_4P_3$	37.0, 20.0	37.9	
17	68	C	41	157–158.5	$C_{20}H_{40}N_9O_4P_3$	28.5, 19.5	38.9	
18	68	C	36	149–150	$C_{20}H_{40}N_9O_4P_3$	27.3, 19.8	38.2	
21	0.5	D	79	149–150	$C_4H_{12}Cl_2N_7P_3$	35.7, 26.0, 14.9	34.0, 34.4, 41.4	
22	78	E	27	145–147.5	$C_6H_{20}N_9P_3$	37.7, 21.1, 17.9	38.3, 38.6, 41.7	
23	18	D	36	96–98	$C_9H_{32}N_{12}P_4$	13.8, 9.7, 9.6	32.6, 44.6	
24	18	D	75	136–138	$C_{10}H_{32}N_{12}P_4$	19.1, 9.5, 9.4	30.5, 42.7	
25	18	D	55	104–106.5	$C_{10}H_{32}N_{12}P_4$	13.8, 9.6	27.2, 33.0, 39.8	–0.1
26	18	D	100	*e*	$C_{10}H_{32}N_{12}P_4$	13.5, 9.5	27.2, 33.1, 39.5	–0.1
27	18	D	56	124–126	$C_{10}H_{32}N_{12}P_4$	13.6, 9.5	32.3	
28	18	D	52	135–137	$C_{10}H_{32}N_{12}P_4$	13.9, 9.6	32.9	
29	42	B	34	206–208	$C_{16}H_{46}N_{12}P_4$	13.3, 9.6, 8.6	36.2, 49.2	
30	42	B	33	>200 dec	$C_{16}H_{44}N_{12}P_4$	19.2, 10.3, 8.5	29.5, 41.4	
31	42	B	24	>200 dec	$C_{16}H_{44}N_{12}P_4$	14.0, 8.6	31.7, 38.9, 43.6	–0.4
32	42	B	100	*e*	$C_{16}H_{44}N_{12}P_4$	12.5, 8.3	33.0, 39.9, 43.5	–0.1
33	42	B	68	198–200	$C_{16}H_{44}N_{12}P_4$	12.8, 9.6	38.3	
34	42	B	32	192–195	$C_{16}H_{44}N_{12}P_4$	13.9, 9.6	39.8	

[a] A = C_6H_6; B = *n*-C_5H_{12}; C = Et_2O; D = CH_2Cl_2–Et_2O; E = CH_2Cl_2. [b] Anal. (C, H, N). [c] Chemical shifts (ppm) positive to low field; coupling constants in Hertz. [d] Purified by sublimation [60 °C (1 mmHg)]. [e] Oily material.

dropwise 20 mL of a 1.5 M solution of $MeNH_2$ in C_6H_6. After warming to room temperature, the reaction mixture was stirred for 3 days. Then, the temperature was raised to 50 °C for 6 h and the precipitated salt was filtered off. Evaporation of the filtrate gave a solid, which afforded 0.13 g of **22** upon recrystallization from CH_2Cl_2. Further data are given in Table V.

$N_4P_4Az(NHMe)_7$ and $N_4P_4Az_2(NHMe)_6$ (23–28). To a stirred solution of one of the precursors $N_4P_4AzCl_7$ or $N_4P_4Az_2Cl_6$ (gem, trans, or cis isomers; 1 mmol, 0.5 g) in 15 mL of C_6H_6, cooled at 5 °C, was added slowly 15 mL of a 2 M solution of $MeNH_2$ in C_6H_6. After warming to room temperature and a reaction time of 18 h, the temperature of the reaction mixture was raised to 50 °C for 6 h. The reaction mixture was filtered off, and evaporation of the filtrate in vacuo gave the crude product. This was purified by recrystallization from CH_2Cl_2–Et_2O. With 1,*cis*-3-$N_4P_4Az_2Cl_6$ as starting material, a contaminated oil was obtained. Mass and NMR spectra indicated the presence of the completely aminolyzed product **26**. Further data are given in Table V.

$N_4P_4Az(NMe_2)_7$ and $N_4P_4Az_2(NMe_2)_6$ (29–34). To a stirred solution of one of the precursors $N_4P_4AzCl_7$ or $N_4P_4Az_2Cl_6$ (gem, trans, or cis isomers; 1 mmol, 0.5 g) in 25 mL of Et_2O, cooled at 0 °C, was added dropwise 15 mL of a 3 M solution of Me_2NH in Et_2O. After warming to room temperature and a reaction time of 18 h, the reaction mixture was filtered off and the filtrate was evaporated in vacuo. The residual oily material was dissolved in 25 mL of Et_2O and the solution refluxed overnight after adding 10 mL of a 3 M solution of Me_2NH in Et_2O. Again, the reaction mixture was filtered off and the filtrate was evaporated in vacuo. The resulting crude product was recrystallized several times from *n*-C_5H_{12}, giving either waxy crystals (**29–31**, **33**, **34**) or an oily substance (**32**). The purity of **32** remained unsatisfactory, probably by inclusion of solvent; mass and NMR spectra were in agreement with the completely aminolyzed product **32**. Further data are given in Table V.

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