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ELECTRONIC INTERACTIONS WITHIN THE MOLECULES OF (1-AZIRIDINYL)CYCLOPHOSPHAZENES WITH AROMATIC SUBSTITUENTS

KRYSTYNA BRANDT

Institute of Polymer Chemistry, Polish Academy of Sciences, 41-800 Zabrze (Poland)

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ABSTRACT

The synthesis and spectral characteristics of the new series of cytostatically active *ortho*- (dioxy- or diaminoarylene) substituted (1-aziridinyl)cyclophosphazenes of general formula $N_3P_3Az_4R_2$, where 2R = *o*-phenylenediamino, 1,1-dioxybinaphthylo-2,2′, and 2,2′-dioxybinaphthylo-1,1′, are described. UV and ^1H NMR spectroscopies have provided evidence for the intramolecular electronic interactions between the aromatic π-electron systems and the lone electron pairs of the 1-aziridinyl groups attached to the same phosphazene rings. The existence of strong hydrogen bonding in the molecules of phenyl(endi)amino(1-aziridinyl)cyclophosphazenes is revealed by IR spectral data.

The recognized intramolecular interactions may be of importance for elucidating the superior cytostatic activity in the studied series of compounds.

INTRODUCTION

The electronic structure of (1-aziridinyl)cyclophosphazene derivatives of the general formula $N_3P_3Az_nR_{6-n}$ (Az means $-NC_2H_4$) was reported to be a main factor governing their alkylating ability towards DNA of tumour cells [1–4]. The cytostatic activity within the series was found to be approximately directly proportional to the electron-donating power of the R substituents, expressed by their basicity constants [3,4].

It may be assumed that electronic effects within a given molecule influence the capacity of 1-aziridinyl groups to convert to the respective carbocations, $-NHCH_2CH_2^+$, this being necessary for alkylating the nucleophilic sites of DNA [1,2,5]. The carbocations might arise from the protonation of the aziridinyl N atoms under physiological conditions [3,7], which could be favoured by the additional electron input from the electrondonating co-substituents attached to the neighbouring P atoms in the same phosphazene ring.

However, to date there has been no experimental evidence for the occurrence of such intramolecular interactions between the lone electron pairs of the azir-

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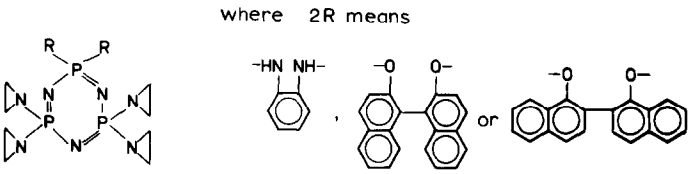
idinyl groups and the electronic systems of the respective R substituents within the series of formula $N_3P_3Az_nR_{6-n}$.

Looking for such evidence we have designed and synthesized the new series of tetrakis(1-aziridinyl)cyclophosphazenes with spirocyclic aromatic substituents at one of the P atoms of general formula A (Scheme 1)



These compounds, by virtue of possessing conjugated π-electron systems, provide a convenient objective for following the respective electronic effects by means of UV and ^1H NMR spectroscopies. In this paper we describe the spectral characteristics of the newly synthesized aromatic tetrakis(1-aziridinyl)cyclophosphazene derivatives, including also those of *gem*-$N_3P_3Az_4(NHPh)_2$, proven to be the most active cytostatic agent within the series studied by Van der Huizen et al. [3] and which has not hitherto been subjected to such spectroscopic investigation.

This is the first time that the experimental techniques such as UV and ^1H NMR spectroscopies, hitherto successfully applied for studying the nature of direct conjugation between a phosphazene ring and various exocyclic aromatic substituents [8–12], have been used for following the indirect electronic interactions between two different (aromatic–heterocyclic) co-substituents within the respective cyclophosphazene molecules.

EXPERIMENTAL

Syntheses

The series of hitherto unreported *ortho*(dioxy- or diaminoarylene) substituted (1-aziridinyl)cyclophosphazenes was synthesized by aziridinolysis of the previously prepared corresponding chloride precursors, according to Scheme 2.

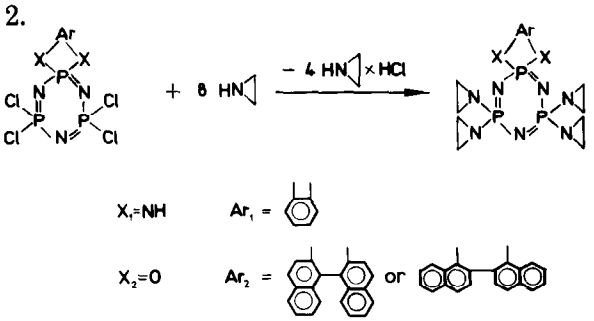
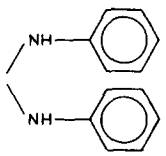
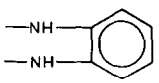
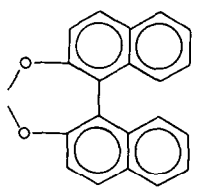
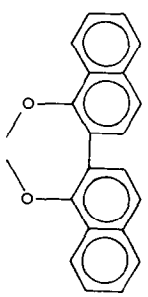


TABLE 1

Cyclophosphazene derivatives of general formula *gem*-$N_3P_3X_4R_2$ discussed in this work

2R	X	Code number	Ref.
2Cl	Cl	**1**	[a]
	Az	**2**	13
2Az	Az	**3**	14
	Cl	**4**	15
	Az	**5**	3
	Cl	**6**	16[b]
	Az	**7**	
	Cl	**8**	17[b]
	Az	**9**	
	Cl	**10**	17[b]
	Az	**11**	

[a]Product of Merck, Darmstadt.
[b]Synthezised for the first time in this work.

For comparative purposes we also resynthesized some of the known aziridinylcyclophos-phazene derivatives, in particular $N_3P_3Az_nCl_{6-n}$ ($n=4,6$) [13,14] and *gem*-$N_3P_3Az_4(NHPh)_2$ [3]. All the (1-aziridinyl)cyclophosphazenes synthesized and their chloride precursors of general formula *gem*-$N_3P_3X_4R_2$ are listed in Table 1.

General synthetic procedure for the preparation of aromatic tetrakis(1-aziridinyl)cyclophosphazene derivatives **5**, **7**, **9** *and* **11**

To a stirred solution of 10 mmol of suitable chloride precursor $N_3P_3R_2Cl_4$ in 70–100 ml of solvent (THF for **5** and **7**; benzene for **9** and **11**), in the case of aryl(endi)amino derivatives cooled to 0–5 °C, a solution of aziridine in the solvent was slowly added dropwise.

In all experiments aziridine was used in at least twofold excess relative to cyclophosphazene chloride functions, which enabled it to serve simultaneously as a reagent as well as HCl scavenger. All the aziridinolysis reactions were performed in the presence of active carbon (Aktivkohle Dartcotm G-60, 100–325 mesh from Aldrich) under a dry argon atmosphere with the exclusion of moisture by calcium chloride drying tubes. In the course of the process the aziridinium chloride formed was filtered off several times from the reaction mixture. After each such operation a new portion of active carbon was added to the filtrate.

The cooling bath, if any, was removed when the addition was completed. The reaction was next carried out for 4–6 h at room temperature until TLC showed the absence of any coloured spots after spraying the developed plates with the pyridine/*m*-toluidine (1:1) detecting reagent (complexing agent for cyclophosphazene chlorides) [17].

After final filtration the solvents and the excess of aziridine, if any, were distilled off under reduced pressure to give the corresponding crude products, which were then crystallized from a mixture of THF/hexane (1:2) (R=(di)aminoaryl(ene), **5**, **7**) or benzene/hexane (1:2) (R=dioxyarylene, **9**, **11**), yielding the respective pure aziridinyl derivatives in the form of colourless crystals. Purified aziridinylcyclophosphazenes could be stored under dry atmosphere for prolonged periods without any changes in appearance and spectral characteristics.

The physical constants, yields, elemental compositions and spectroscopic data of compounds **5**, **7**, **9**, **11** are shown in Tables 2 and 3, respectively.

Mass spectroscopy

The mass spectra were recorded on an LKB-900 mass spectrometer at 70 eV electron energy and at an ion source temperature of 250–300 °C.

RESULTS AND DISCUSSION

Mass spectra

The same fragmentation route involving the successive loss of one to four aziridinyl groups from the respective molecular ions was observed for all the

TABLE 2

Physicochemical data for tetrakis(1-aziridinyl)cyclophosphazenes of general formula $N_3P_3Az_4R_2$ (A type)

Compound	Yield (%)		T^c °C	Molecular mass		Elemental composition (%)								IR (in KBr) (cm^{-1})				
	Crude[a]	Cryst.[b]		Exp.[d]	Calc.	C		H		N		P		CH_2	-N< |	P=N	C-$H_{ar.}$	NH[e]
						Exp.	Calc.	Exp.	Calc.	Exp.	Calc.	Exp.	Calc.					
5	72	61	179	$C_{20}H_{28}N_9P_3$ 487	487	42.16	42.28	5.81	5.74	25.69	25.87	19.01	19.09	1080 1444 1480 2992	928 1272	1172 1215	1500 1604	3236 br 3356 sh
7	88	75	238	$C_{14}H_{22}N_9P_3$ 409	409	41.02	41.07	5.43	5.37	30.68	30.80	22.79	22.73	1084 1440 1485 2992	936 1268	1188	1496 1608 3070	3160 br 3380 sh
9	95	86	239	$C_{28}H_{28}O_2N_7P_3$ 587	587	57.48	57.24	4.56	4.77	16.25	16.69	15.35	15.84	1072 1440 1485 2996	940 1268	1188 1244	1500 1604 3016 3068	
11	93	82	234	$C_{28}H_{28}O_2N_7P_3$ 587	587	57.32	57.24	4.83	4.77	16.72	16.69	15.64	15.84	1080 1444 1480 2992	940 1264	1180 1216	1504 1600 3024 3068	

[a]Yield of crude product. [b]Yield of crystallized product. [c]Temperature of an exothermic effect on DSC curve. [d]Value according to mass spectrum. [e]br, broad; sh, sharp.

TABLE 3

UV and NMR data for the A-type derivatives $N_3P_3Az_4R_2$

Compound	UV		^{1}H NMR δH (ppm)			Solvent[a]	^{31}P NMR AB_2 spin system		
	λ_{max} (nm)	ϵ_{max}	$(CH)_{Ar}$	H_2C —— CH_2 (N)	N-H		δPR_2[b]	δPAz_2[c]	J_{P-P} (Hz)
5	282	2.4×10^4	7.12 (s)	2.09 (d)	4.84 (s)	*d*-Methanol	8.32	32.38	36.30
7	294	5.3×10^3	6.61 (s)	2.09 (d)	4.85 (s)	*d*-Methanol	25.25	39.26	35.87
			6.49 (s)	1.92 (d)	2.63 (s)	*d*-THF	24.27	38.52	41.30
9	307	1.7×10^4	7.18-7.95 (m)	2.10 (d)		*d*-Chloroform	28.86	40.32	51.18
11	260	9.8×10^4	7.20-8.22 (m)	2.10 (d)		*d*-Chloroform	30.97	39.63	51.18

[a]The same solvent was used for both ^{1}H and ^{31}P NMR measurements. [b]Center of the triplet. [c]Center of the doublet.

studied tetrakis(1-aziridinyl)cyclophosphazene derivatives of formula *gem*-$N_3P_3Az_4R_2$ (Table 4).

In the case of *spiro*(dioxy- or diamino)arylene(1-aziridinylcyclophosphazenes) **7**, **9**, **11** the fragmentation pattern presented above was the only one worthy of consideration, whereas for *gem*-$N_3P_3Az_4(NHPh)_2$ (**5**) in the major fragmentation route the loss of one of four aziridinyl groups was preceded by the initial splitting of the one $-NHC_6H_5$ (R) substituent from the molecular ion and consequently following peaks were observed due to that (besides those listed in Table 4): *m/z*, fragment, intensity: 487 (M^+), 100%; 395 (M^+-R), 40.7%; 352 (M^+-R-Az), 72.7%; 312 ($M^+-R-2Az$), 40.7%; 270 ($M^+-R-3Az$), 5.9%; 228 ($M^+-R-4Az$), 4.6%.

IR spectra: spectroscopic evidence for the existence of hydrogen bonding in aryl(endi)amino derivatives

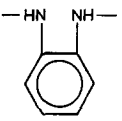
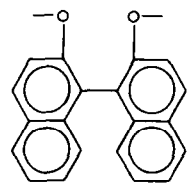
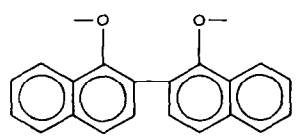
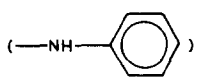
IR spectral data for all new (1-aziridinyl)cyclophosphazene derivatives are shown in Table 2.

In Table 5 is presented spectroscopic evidence for the existence of hydrogen bonding in tetrakis(1-aziridinyl) [(*o*-phenylenediamino) and bis(phenylamino)] cyclophosphazenes (**5**, **7**) and their chloride precursors (**4**, **6**).

It can be seen that the IR spectra of all the (1-aziridinyl) and chloro derivatives in the solid state show two strong peaks in the NH stretching region. Lower frequency peaks are broad and can be attributed to the polymeric-type

TABLE 4

General fragmentation route for *gem*-$N_3P_3Az_4R_2$ Compounds A, Scheme 1

Compound	T^a (°C)	2R	Fragmentation[b], *m/z*				
			M^+	M^+-1Az	M^+-2Az	M^+-3Az	M^+-4Az
7	250		409 (100)	366 (88,2)	325 (8,4)	282 (8,6)	240 (7,1)
9	300		587 (66,3)	546 (20,8)	505 (11,0)	461 (8,5)	420 (7,1)
11	300		587 (53,3)	545 (32,7)	504 (39,1)	461 (12,3)	420 (11,3)
5	250	2 	487 (100)	444 (8,1)	402 (28,2)	362 (9,01)	320 (2,76)

[a]Temperature of ion source. [b]Percentage relative intensity for each fragment is given in parentheses.

intermolecular H bonds [18]. Such bonds might be formed, for example, between NH groups of the respective phenyl(endi)amino substituents and the phosphazene ring nitrogen atoms of the adjacent molecules, as reported previously for [alkylene-diamino]tetrachlorocyclophosphazenes [19]. Higher frequency sharp peaks, following the Allcock's interpretation for $N_3P_4Cl_4[o\text{-}C_6H_6(NH)_2]$ might be attributed to freer NH groups [16,20].

However, in general absolutely free X–H stretching absorption bands are considered to appear only when compound is examined in a gas phase or in a very dilute solution in non-polar solvent [18,21]. Sharp bands may also result for instance from intramolecular hydrogen bonds. Such a phenomenon is reported for the molecule of $N_3P_3[NH(CH_2)_2NH](NMe_2)_2$) [22]. On the other hand they might be due to the dimeric intermolecular H bonds between two adjacent cyclophosphazene molecules [19].

TABLE 5

IR spectral evidence for H bonding in tetrakis(1-aziridinyl)[aryl(endi)amino]cyclophosphazenes and their respective chloro precursors

No.	Compound	Position of NH bands[a] ν (cm^{-1})					
		In solid state KBr mull		In solution			
				$CHCl_3$		THF	
		Band I	Band II	Band I	Band II	Band I	Band II
7	$N_3P_3[o\text{-}C_6H_4(NH)_2]Az_4$	3160 br	3380 sh		3452 sh		3588 br
5	*gem*-$N_3P_3(NHC_6H_5)_2Az_4$	3236 br	3356 sh		3412 sh	3272 br weak	3512 br intense
6	$N_3P_3[o\text{-}C_6H_4(NH)_2]Cl_4$	3268 br	3364 sh	insoluble in $CHCl_3$			3582 br
4	*gem*-$N_3P_3(NHC_6H_5)_2Cl_4$	3235 br	3396 sh		3402 br intense	3204 br intense	3576 br weak

[a]br, broad; sh, sharp.

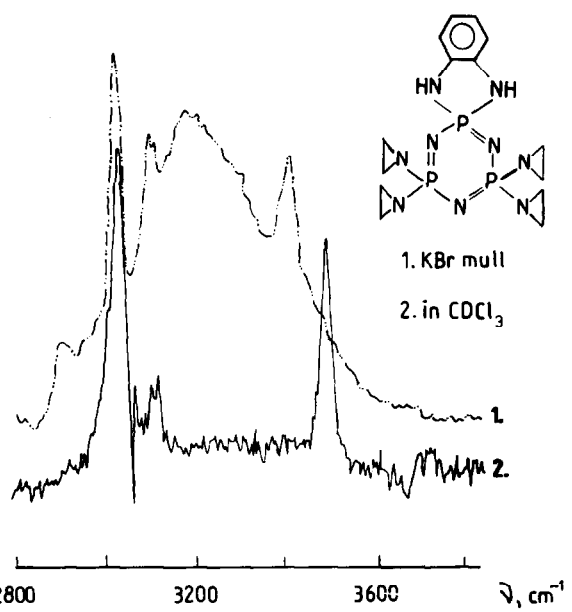


Fig. 1. Comparison of the IR spectra of $N_3P_3Az_4$-[*o*-phenylenediamino] (**7**) in the solid state (1) and in $CDCl_3$ solution (2), showing evidence for hydrogen bonding in the solid state.

In the spectra of chloroform solutions only the sharp peaks are visible; they are shifted to higher frequencies relative to those in the solid state (Table 5, Figs. 1, 2). Figure 3 shows in its turn the comparison of the IR spectra in the solid state of $N_3P_4[o\text{-}(NH)_2C_6H_4]Az_4$ (**7**) and its chloro precursor (**6**). The

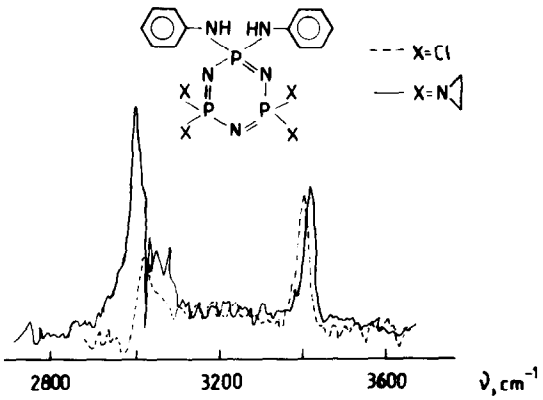


Fig. 2. Comparison of the positions of the NH stretching bands in the IR spectra of $N_3P_3(NHPH)_2Cl_4$ (broken line) and $N_3P_3(NHPH)_2Az_4$ (solid line). The spectra taken were of chloroform solutions of the samples with compensation for the solvent.

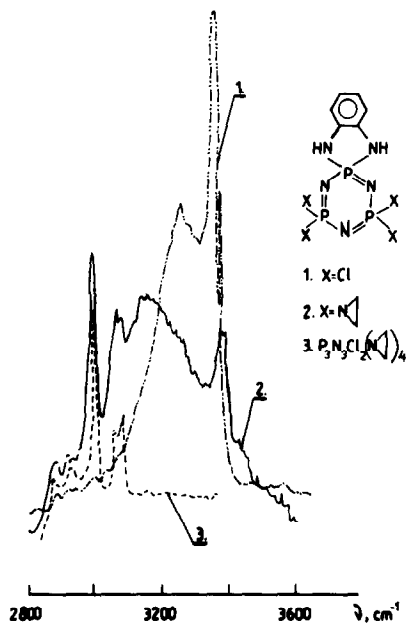


Fig. 3. NH- stretching bands in the spectra of the chloro (**1**) and the (1-aziridinyl)-substituted (**2**) [*o*-phenylenediamino]cyclophosphazene derivatives.

spectrum of NH-free $N_3P_3Cl_2Az_4$ (**2**) is used as a reference standard.

At the present stage of our investigations it is not possible to make unambiguous assignments of the various NH stretching bands. Because of the importance of hydrogen bonding in the interaction between the cytostatic agents

and DNA molecules, further studies, in particular on solvent- and temperature-dependence of the discussed IR spectra are underway.

^{31}P *NMR spectra*

All new (1-aziridinyl)cyclophosphazenes $N_3P_3Az_4R_2$ (compounds "A", Scheme 1) show AB_2 spin systems in ^{31}P NMR spectra. A typical shape of this spectrum is shown in Fig. 4 (2R=*o*-phenylenediamino).

From all spectra observed the parameters $\delta_{P(A)}$, $\delta_{P(B)}$ and $J_{P\text{-}P}$ (Table 3) could be readily obtained by direct analysis via well known approximations [23].

UV and ^1H NMR spectra: spectral evidence for the occurrence of electronic interactions between (1-aziridinyl) and di(amino or oxy) arylene substitutents in the respective cyclophosphazene derivatives

Whilst the direct electronic interference between N_3P_3 ring and aryl [8,10,12,24] or aryl(endi)(oxy or amino) substituents [3,9,11,16] has been widely investigated, to the best of our knowledge there have hitherto been no reports about the indirect electronic interactions between various substituents attached to different phosphorus atoms in the N_3P_3 ring.

We have found the existence of such interactions in the case of phenyl(endi)amino containing (1-aziridinyl)cyclophosphazenes **5** and **7** and

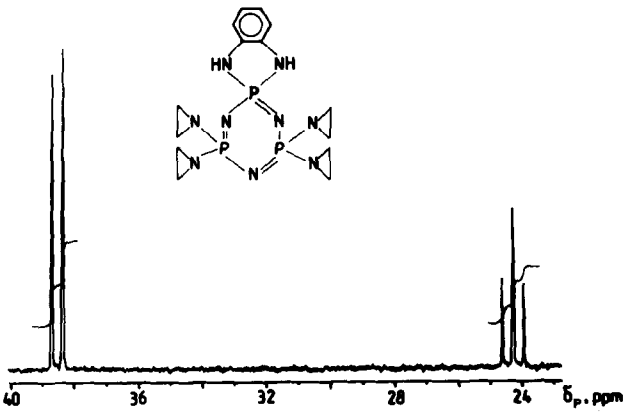
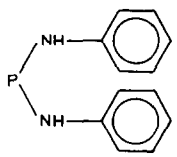
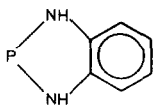
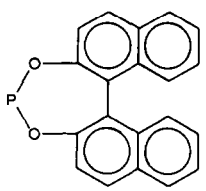
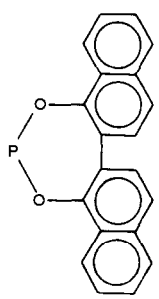


Fig. 4. ^{31}P NMR spectrum of [*o*-phenylenediamino]$N_3P_3Az_4$ (**7**), a typical example of the A_2B spin system.

TABLE 6

Comparison of UV absorption maxima for the corresponding pairs of chloro and 1-aziridinyl cyclophosphazene derivatives

$N_3P_2X_4PR_2$			UV Data			
PR_2	X	No.	λ_{max} (nm)	$\Delta\lambda_{max}$[a] (nm)	ϵ_{max}	$\Delta\epsilon_{max}$[b]
	Cl	**4**	274	8	2.2×10^4	2.0×10^3
		**5**	282		2.4×10^4	
	Cl	**6**	286	8	4.5×10^3	8.0×10^3
		**7**	294		5.3×10^3	
	Cl	**8**	305	2	1.35×10^4	1.0×10^3
		**9**	307		1.45×10^4	
	Cl	**10**	258	2	1.10×10^5	-1.0×10^4
		**11**	260		1.00×10^5	

[a] $\Delta\lambda_{max} = \lambda_{max}(X=Az) - \lambda_{max}(X=Cl)$. [b] $\Delta\epsilon_{max} = \epsilon_{max}(X=Az) - \epsilon_{max}(X=Cl)$.

also, although to a somewhat smaller extent, for both the obtained binaphthylenedioxy(1-aziridinyl)cyclophosphazene derivatives **9** and **11** (Table 6).

The substituents' electronic interactions are clearly visible from comparison of the UV spectra for the discussed phenylamino and (*ortho*-phenylenediamino) substituted (1-aziridinyl)cyclophosphazenes (**5**, **7**) and their respective chloroprecursors (**4**, **6**) (Fig. 5). The spectrum of *gem*-$N_3P_3Az_4Cl_2$ (**2**) is placed in the same figure in order to visualize that, as previously reported

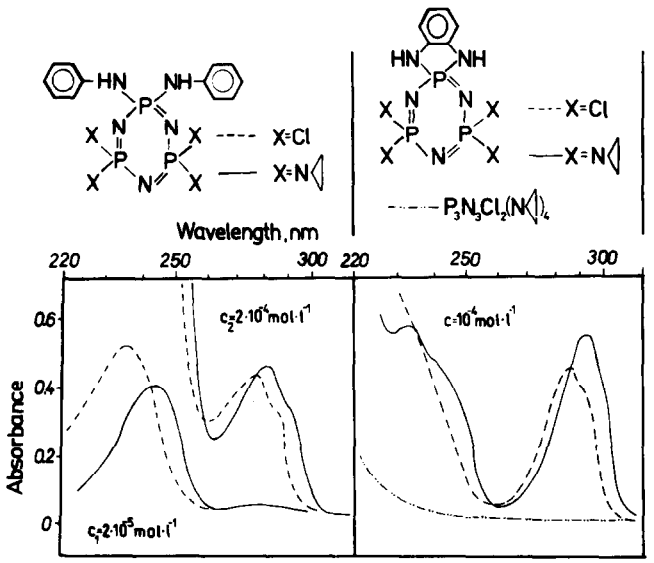


Fig. 5. Comparison of the UV spectra of two pairs of the analogous tetrachloro (broken line) and tetrakis(1-aziridinyl) (solid line) phenyl(endi)amino cyclophosphazene derivatives showing evidence for intramolecular electronic interactions between the aziridinyl groups and the respective phenyl(endi)amino substitutents.

[9], neither N_3P_3 ring itself nor its chloro, nor (1-aziridinyl) substituents absorb UV light in the wavelength region considered (the latter compound is completely UV transparent at $\lambda > 230$ nm). Thus derivatives **4**–**7** are UV absorbers only by virtue of containing the corresponding aromatic chromophores: bis(phenylamino) for **4** and **5**; (*o*-phenylenediamino) for **6** and **7**.

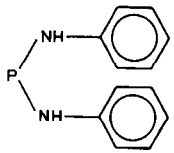
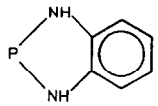
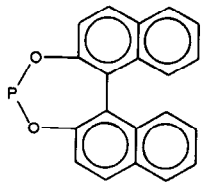
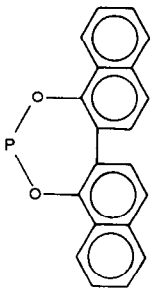
Therefore the UV spectra of the analogous chloro and (1-aziridinyl)cyclophosphazenes having the same aromatic units could be expected to overlap. However, the overlapping does not occur and the UV absorption maxima of both (1-aziridinyl) derivatives **5** and **7** presented in Fig. 5 are shifted towards longer wavelengths and higher intensities related to those of their respective chloro precursors, **4** and **6**.

Considering the UV transparency of (1-aziridinyl) groups themselves indicated above, the observed differences in the spectra can be attributed only to electronic interactions between the lone electron pairs of (1-aziridinyl) N atoms and the π-electron systems in the corresponding aromatic rings linked via NH group(s) to the same N_3P_3 cycle.

The conclusions drawn from the comparative studies of the UV spectra for compounds **4** and **5**, **6** and **7**, have been confirmed by the similar comparison of the respective pairs of ^{1}H NMR spectra (Table 7, Figs. 6 and 7). In both cases the resonance signals of aromatic protons, which for chloro-derivatives (**4**, **6**) exhibit more (**4**, Fig. 6) or less (**6**, Fig. 7) well resolved multiplets, after

TABLE 7

^{1}H NMR data for the corresponding *gem*-tetrachloro and tetrakis(1-aziridinyl)cyclophosphazenes of general formula $N_3P_2X_4PR_2$

Compound			^{1}H NMR δ_H (ppm)			
PR_2	X	No.	$(CH)_{Ar}$	H_2C—CH_2 (N)	N-H	Solvent
	Cl	**4**	7.02, 7.25 (2m)		5.52 (s)	*d*-Methanol
		**5**	7.12 (s)	2.09 (d)	4.84 (s)	*d*-Methanol
	Cl	**6**	7.46 (m) 8.07 (d)		5.00 (s) 6.70 (s)	*d*-Methanol *d*-THF
		**7**	6.61 (s) 6.49 (s)	2.09 (d) 1.92 (d)	4.85 (s) 2.63 (s)	*d*-Methanol *d*-THF
	Cl	**8**	7.20–7.52 (m) 7.85–8.02 (m)			*d*-Chloroform
		**9**	7.18–7.36 (m) 7.81–7.95 (m)	2.10 (d)		*d*-Chloroform
	Cl	**10**	7.19–8.26 (m)			*d*-Chloroform
		**11**	7.20–8.22 (m)4	2.10 (d)		*d*-Chloroform

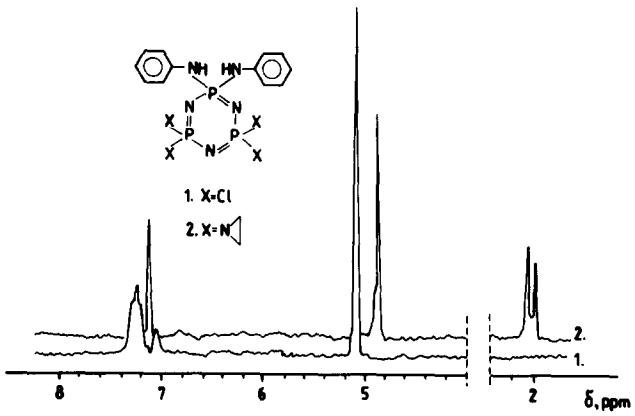


Fig. 6. Comparison of ^{1}H NMR spectra (in *d*-methanol) of bis(anilido)cyclophosphazene derivatives with chloro and (1-aziridinylo) substituents.

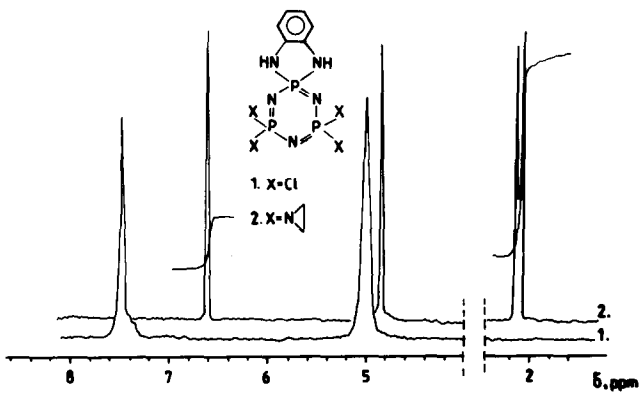


Fig. 7. Comparison of the ^{1}H NMR spectra (in *d*-methanol) of spiro[*o*-phenylenediamino]cyclophosphazene derivatives with chloro and (1-aziridinylo) substituents.

replacing Cl with (1-aziridinyl) substituents shift upfield and convert into sharp singlets. This reflects the increased shielding effect upon aromatic protons due to the electronic interactions between the π electrons of the phenyl(ene) rings, and the lone electron pairs of the corresponding Az substituents; it is particularly visible for the [*o*-phenylenediamino] derivatives where the differences in chemical shifts of the chloro (**6**) and 1-aziridinyl (**7**) analogues are very profound (Fig. 7, Table 7).

With regard to dioxybinaphthylene derivatives the bathochromic shifts and hyperchromic effects of (1-aziridinyl) substituted compounds (**9, 11**) relative to their chloro analogues observed in the UV spectra (Fig. 8, Table 6) are also

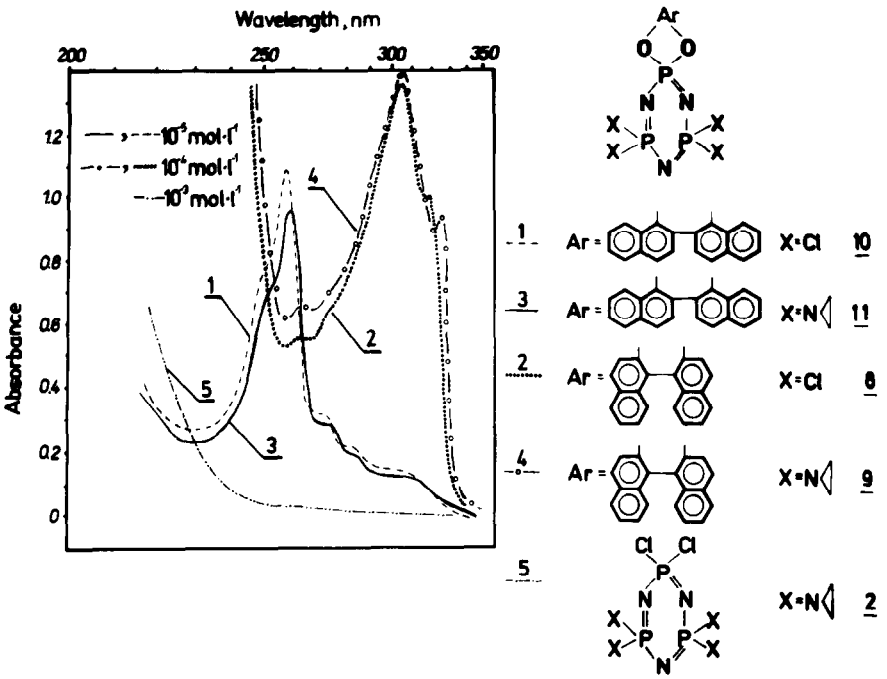


Fig. 8. Comparison of the UV spectra of the isomeric spiro[1,1′-dioxybinaphthylo-2,2′] and spiro[2,2′-dioxybinaphthylo]-tetrachlorocyclophosphazenes (**8** and **10** respectively) and their respective tetrakis(1-aziridinyl) derivatives (**9** and **11** respectively) with the UV spectrum of the reference chromophore-free tetrakis(1-aziridinyl)dichlorocyclophosphazene (**2**).

accompanied by noticeable changes in the shape and position of the corresponding aromatic protons' ^{1}H NMR signals (Table 7). In this case, because of the absence of active hydrogens in the molecules of the respective (1-aziridinyl) derivatives **9**, **11**, the intramolecular electronic interactions between the (1-aziridinyl) and the respective isomeric dioxybinaphthylene substituents must proceed with the participation of the electrons of the corresponding N_3P_3 ring.

CONCLUSIONS

Both the UV and ^{1}H NMR spectra reveal the existence of intramolecular electronic interactions between the lone electron pairs of aziridinyl groups and the conjugated π-electron systems of the corresponding di(oxy- or amino)aryl(ene) substituents attached to the same cyclotriphosphazene ring.

These electronic effects probably result in the increased capacity of Az groups to form carbocations: $NHCH_2CH_2^+$ capable of alkylating the nucleophilic sites of DNA; the latter reaction being reported [1,7] as responsible for the cytostatic properties of 1-aziridinyl-containing drugs.

Preliminary in vitro screening has shown all the studied aromatically substituted tetrakis(1-aziridinyl)cyclophosphazene derivatives **5**, **7**, **9**, **11**, to be

more cytostatically active than the reference hexakis(1-aziridinyl)cyclophosphazene (**3**) [25]. Further studies on the electronic structure–cytostatic activity relationship are underway.

REFERENCES

1 J.-F. Labarre, Top. Curr. Chem., 102 (1982) 1.
2 G. Guerch, J.-P. Faucher, M. Graffeuil, G. Levy and J.-F. Labarre, J. Mol. Struct., 88 (1982) 317.
3 A.A. Van der Huizen, J.C. Van de Grampel, W. Akkermann, P. Lelieveld, A. Van der Meerkalverkamp and H.B. Lamberts, Inorg. Chim. Acta, 78 (1983) 239.
4 J.C. Van de Grampel, A.A. Van der Huizen, A.P. Jekel, J.W. Rusch, T. Wilting, W. Akkermann and P. Lelieveld, Phosphorus Sulph., 18 (1983) 337.
5 J.-F. Labarre, J.-P. Faucher, G. Levy, F. Sournies, S. Cros and G. Francois, Eur. J. Cancer, 15 (1979) 637.
6 O.C. Dermer and G.E. Ham, Ethyleneimine and Other Aziridines, Academic Press, New York, 1969.
7 A.A. Van der Huizen, Ph.D. Thesis, University of Groningen, The Netherlands, September 14, 1984, p. 6.
8 A.J. Wagner and T. Moeller, J. Inorg. Nucl. Chem., 33 (1971) 1307.
9 B. Lakatos, A. Hesz, Zs. Vetessy and G. Horwath, Acta Chim. Acad. Sci. Hung., 60 (1969) 309.
10 T. Chivers and N.L. Paddock, Inorg. Chem., 1 (1971) 848.
11 K. Brandt and W. Kasperczak, Spectrochim. Acta, 38A (1982) 961.
12 P.J. Harris, K.B. Williams and B.L. Fisher, J. Org. Chem., 49 (1984) 406.
13 G. Ottmann, H. Agahigian, H. Hooks, G.D. Vickiers, E. Kober and R. Ratz, Inorg. Chem., 3 (1964) 753.
14 R. Ratz, E. Kober, Ch. Grundmann and G. Ottmann, Inorg. Chem., 3 (1964) 757.
15 V.B. Desai, R.A. Shaw and B.C. Smith, J. Chem. Soc., A, (1970) 2023.
16 H.R. Allcock and R. Kugel, Inorg. Chem., 5 (1966) 1016.
17 K. Brandt and Z. Jedlinski, J. Org. Chem., 45 (1980) 1672.
18 A.D. Cross and R.A. Jones, in: An Introduction to Practical Infrared Spectroscopy, 3rd edn, Butterworths, London, 1969, p. 43.
19 G. Guerch, M. Graffeuil, J.-F. Labarre, R. Enjalbert, R. Lahana and F. Sournies, J. Mol. Struct., 95 (1982) 237.
20 H.R. Allcock and E.J. Walsh, Inorg. Chem., 10 (1971) 1643.
21 M.M. Coleman, K.H. Lee, D.J. Skrovanek and P.C. Painter, Macromolecules, 19 (1986) 2149.
22 Y.S. Babu, H. Manohar, K. Ramachandran and S.S. Krishnamurthy, Z. Naturforsch., Teil B 33 (1978) 558.
23 R.A. Hoffman, S. Forsen and B. Gestblom, in P. Diehl, E. Fluck and R. Kosfeld (Eds.), NMR-Basic Principles and Progress, Springer-Verlag, Berlin-Heidelberg-New York, 1971, p. 104.
24 Ch.W. Allen and A.J. White, Inorg. Chem., 13 (1974) 1220.
25 D. Duś, K. Brandt, E. Gebarowska, E. Wojdat, Z. Jedliński and Cz. Radzikowski, Arch. Immunol. Ther. Exper., to be published.