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Anomalous NMR Behavior of Meso Compounds with Remote Stereogenic Centers on Addition of Chiral Shift Reagent or Chiral Solvating Agent

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Abstract: A problem has arisen in using chiral shift reagents (CSR) and chiral solvating agents (CSA) to determine meso and racemic forms of diastereoisomers in which the stereogenic centers of the molecules are separated by achiral spacers. It is found that NMR signals of both meso and racemic forms of diastereoisomers may exhibit doubling on addition of CSR/CSA, which means that unequivocal assignments cannot be made without characterizing the effects for separate meso and racemic forms; this is particularly important for additions of CSR/CSA at relatively low concentrations, which always result in the splitting of some NMR signals of diastereoisomers. The phenomenon is demonstrated in the ^{31}P NMR spectra of meso and racemic forms of three spermine-bridged *gem*-disubstituted cyclotriphosphazatrienes, **1a**−**c**, and compared with analogous achiral molecules, the per-substituted spermine-bridged cyclotriphosphazatrienes **2a**−**d**. As expected, only one set of ^{31}P NMR signals was observed for the achiral compounds **2a**−**d**, even on addition of CSA. Two sets of ^{31}P NMR ABX multiplets corresponding to meso and racemic diastereoisomers were observed for compounds **1a**−**c**; on addition of CSA, the signals of at least one of the multiplets for each compound separated into more than the expected groups of three lines with an intensity distribution of 2:1:1. To understand this phenomenon, the meso and racemic forms of **1a** and **1b** and the meso form of **1c** have been separated and characterized by X-ray crystallography. On addition of CSA to the racemic forms of **1a** and **1b**, the ^{31}P NMR spectrum shows the expected doubling of signals, but, unexpectedly, the same is observed for each of the meso forms of **1a**−**c**. Analogous results using both CSA and CSR have been obtained for the meso and racemic forms of the diastereoisomeric piperazine-bridged macrocyclic-phosphazene compound, **3**, whereas no effect was observed for the two meso forms of the doubly bridged macrocyclic-phosphazene compound **4**. The phenomenon of doubling of the ^{31}P NMR signals of the meso form of singly bridged cyclotriphosphazatrienes, **1a**−**c** and **3**, is explained by consideration of the equilibrium in solution of independent complexation of a chiral ligand with molecules that have two chiral cyclophosphazene moieties separated by an achiral spacer group. The results show that the stereogenicity of such diastereoisomeric molecules in solution cannot be characterized unequivocally by NMR measurements on addition of either CSR or CSA.

Introduction

Chiral shift reagents (CSR)[1] and chiral solvating agents (CSA)[2] have been used extensively in NMR spectroscopy to characterize the chiral properties of molecules in solution. Both rely on the equilibrium complexation of a chiral ligand with a chiral molecule, resulting in different NMR spectra being observed for enantiomers. CSR/CSAs have been used qualitatively to demonstrate the existence of optical isomers, quantitatively to assist in determinations of enantiomeric excess, and analytically, on occasion, to assign the absolute configuration of particular enantiomers.[1,2] Few problems are experienced in the use of CSR/CSAs, except that chiral molecules need to be soluble in nonpolar solvents and different CSR/CSAs may need to be tried to optimize the effect. In the general literature,[1,2] CSRs are preferred as they result in greater effects at lower concentrations than CSAs, although CSRs have to be titrated in more carefully to observe the separation of signals of enantiomers before being masked by line broadening due to

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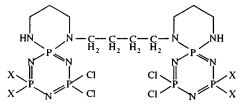
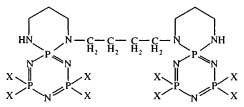
Scheme 1



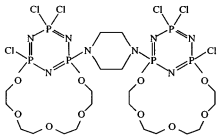
1 (meso + racemate)



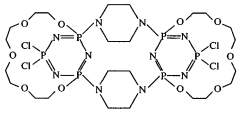
2 (achiral)

	X
1a	phenyl
1b	t-Bu-NH
1c	O-$(CH_2)_3$-O

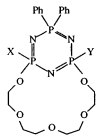
	X
2a	phenyl
2b	t-Bu-NH
2c	O-$(CH_2)_3$-O
2d	Cl



3 (meso + racemate)



4 (meso + meso)



5

X	Y		
Cl	Cl	**5a**	meso
NHPh	NHPh	**5b**	meso
OPh	OPh	**5c**	meso
OPh	NHPh	**5d**	racemate

paramagnetic effects of the lanthanide ion in the complex. Few problems are experienced in the interpretation of the results; NMR signals of racemic mixtures split into two lines of equal intensity corresponding to the separate enantiomers, whereas NMR signals of meso compounds should be unaffected (except for small changes of chemical shift due to addition of CSR/CSA). A problem has arisen in using CSR/CSAs to determine meso and racemic forms of diastereoisomers in which the chiral centers of the molecules are separated by achiral spacers. The phenomenon is demonstrated in the ^{31}P NMR spectra of meso and racemic forms of singly bridged cyclotriphosphazatriene derivatives. The structures of all molecules used in this study are summarized in Scheme 1.

Tetracoordinated phosphorus atoms in cyclophosphazenes $(NPXY)_n$ are pentavalent and potential stereocenters. The possibility of optical isomerism was first discussed in a review[3] about 40 years ago, but the stereogenic properties of substituted cyclophosphazenes have not been investigated until recently.[4−7] For example, it was found that the ^{31}P NMR spectra of *gem*-disubstituted spermine-bridged cyclophosphazene compounds **1a**−**c** [**1a**, X = Ph; **1b**, X = NHBu^t; **1c**, X_2 = O$(CH_2)_3$O] are observed as two sets of AMX spin systems in a 1:1 ratio with a small chemical shift separation consistent with the existence of both meso and racemic forms; this was confirmed for compound **1a** by separation of the diastereoisomers and characterization of both forms by X-ray crystallography.[5] It has also been confirmed by X-ray crystallography that the piperazine-bridged macrocyclic-phosphazene compound **3** exists in both meso and racemic forms and that ^{31}P NMR with addition of the chiral shift reagent, Eu(tfc)$_3$, indicates that they are diastereoisomers.[6] The existence of meso and racemic forms for singly bridged cyclophosphazene derivatives such as **1a**−**c** and **3** explains the observed ^{31}P NMR spectra of two sets of AMX spin systems in a 1:1 ratio with a small chemical shift separation observed previously for lower members of the series of diamine-bridged macrocyclic-cyclophosphazene compounds, $\Delta\delta$ of ca. 0.02−0.05 ppm,[8] and for two analogous series of singly bridged cyclotriphosphazatriene-diamine derivatives (denoted as 3*n*3 and 4*n*4 series with n = 6,7,8,9) by Labarre et al.[9]

The singly bridged cyclophosphazene compounds (e.g., **1**, X ≠ Cl; **3**) exhibit stereoisomerism, because the three phosphorus atoms of each cyclophosphazene ring have different substitution patterns, and those that are part of the >P(bridge) are stereogenic; that is, there are *R* and *S* forms. There are two stereogenic centers in each singly bridged phosphazene compound, **1a**−**c** and **3**, giving rise to diastereoisomers, which exist as 1:1 mixtures of meso (*RS*/*SR*) and racemic (*RR*/*SS*) forms because the cyclophosphazene rings have the same substitution patterns. NMR characterization of the mixture of meso and racemic forms in solution relies on the assumption that addition of CSR or CSA causes the signals of the racemate to separate into two signals of equal intensity, whereas signals of the meso form do not. Problems have arisen in the application of these assumptions to analyze the ^{31}P NMR signals of compounds **1a**−**c**, **3**. On addition of CSR to the NMR solution of compound **3**, separation of signals into meso and racemic forms (with 2:1:1 intensity ratios) was observed for the ^{31}P NMR multiplets of the PCl_2 groups (expanded spectrum shown in Figure 6 of ref 6), whereas the P(OR)Cl group showed more than the expected number of signals.[6] A similar complication was noted for compounds **1a**−**c**, as addition of the chiral solvating agent, (*S*)-(+)-2,2,2-trifluoro-1-(9′-anthryl)ethanol, gave rise to more signals than expected.[5] This meant that the meso and racemic forms of **1b** and **1c** could not be unequivocally assigned by NMR spectroscopy, whereas those for **1a** could be assigned because the separate meso and racemic forms had been characterized by X-ray crystallography.[5]

This paper reports an investigation of the phenomenon that more NMR signals than expected may be observed on addition of CSR/CSA to solutions of singly bridged cyclophosphazene compounds. Results for diastereoisomeric spermine-bridged cyclophosphazenes **1a**−**c** are compared with achiral analogues, **2a**−**d**, and results for the diastereoisomeric singly bridged macrocyclic-phosphazene compound **3** are compared with the two meso forms of the doubly bridged macrocyclic-phosphazene compounds **4a**,**b**. The anomalous NMR behavior observed for meso forms of bridged cyclophosphazenes is explained in terms of the equilibrium complexation of the chiral ligand with molecules having chiral centers separated by achiral spacer groups. These results are contrasted with those for phosphazene derivatives, which behave as expected on addition of CSA to meso (**5a**−**c**) and racemic (**5d**) forms.

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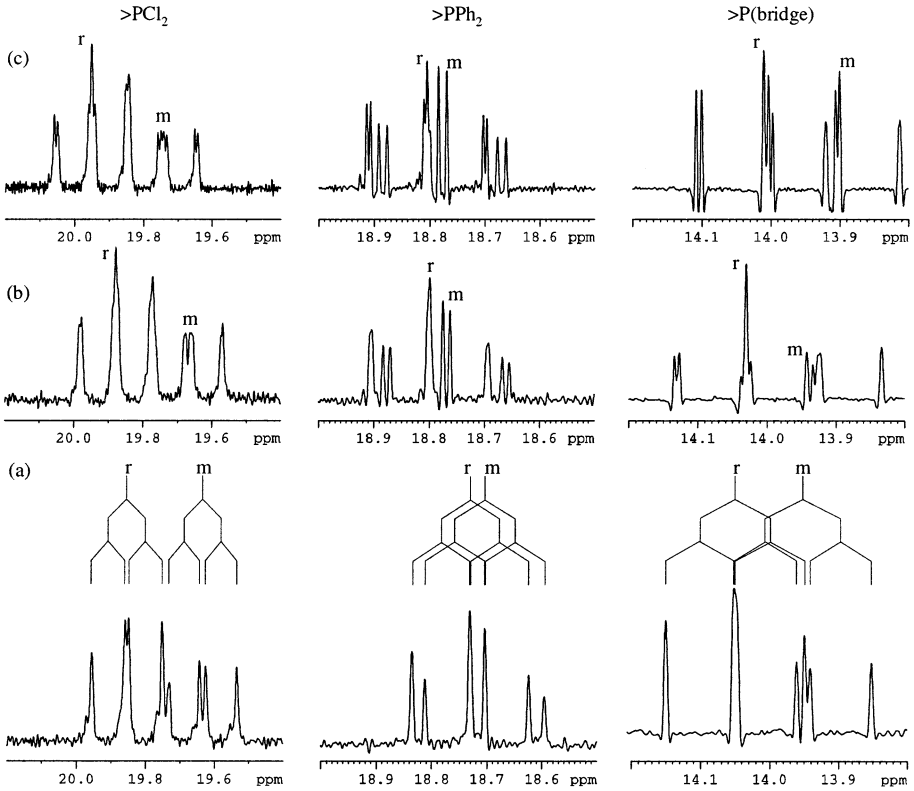

Figure 1. 200 MHz proton-decoupled ^{31}P NMR spectra of compound **1a** in toluene-d_8 solution at 298 K. (a) The two sets of expanded ABX signals correspond to racemic (r) and meso (m) diastereoisomers in the ratio of ca. 60:40. Addition of the chiral solvating agent, (*S*)-(+)-2,2,2-trifluoro-1-(9′-anthryl)ethanol, in a (b) ~5:1 and (c) ~10:1 mole ratio.

Results

The proton-decoupled ^{31}P NMR spectra of **1a**−**c**, **3** in $CDCl_3$ solution are observed as pairs of ABX (or AMX) spin systems, consistent with the existence of meso and racemic forms with small chemical shift differences between NMR signals of the diastereoisomers.[5,6] It was thought that the ^{31}P NMR signals of meso and racemic forms of the piperazine-bridged cyclophosphazene-macrocyclic compound **3** could be assigned by addition of the chiral shift reagent, Eu(tfc)$_3$, because signals for the racemate should separate into two lines in a 1:1 ratio, whereas those for the meso compound should not.[6] Such behavior was observed for the ^{31}P NMR multiplets of the PCl_2 groups (expanded spectrum shown in Figure 6 of ref 6). However, ^{31}P NMR multiplets of the P(OR)Cl group of **3** showed more than the expected number of signals. Although the phenomenon was not understood (or commented upon) at the time, it did not affect the conclusions about the mechanism of the reactions because the stereogenicity of the molecules was based on X-ray crystallographic evidence.[6] Similar anomalous NMR behavior is observed for spermine-bridged cyclophosphazene compounds **1a**−**c** in this work. On addition of the chiral solvating agent,[2] (*S*)-(+)-2,2,2-trifluoro-1-(9′-anthryl)ethanol, to solutions of compounds **1a**−**c**, it is found that the signals of at least one of the ^{31}P NMR multiplets, usually the P(bridging group), split into more lines than was expected for the meso and racemic mixture, that is, more than the three groups of four lines with intensities of ca. 2:1:1. An example is shown for compound **1a** in Figure 1a, in which the ratio of racemic (r) and meso (m) diastereoisomers was adjusted to ca. 60:40 for convenience of following the ^{31}P NMR signals. Unequivocal assignment of signals was made previously by comparison with those for the separate meso and racemic isomers.[5] Addition of CSA in a ~5:1 mole ratio in Figure 1b results in a doubling of one set of signals (meso!) of the PPh_2 group to ca. 18.8 ppm and the P(bridge) to ca. 14 ppm for the racemate. Further addition of CSA to ~10:1 mole ratio in Figure 1c shows more than the expected eight lines for signals of the PCl_2 (>13), P(bridge) (>9), and PPh_2 (>12) groups. Similar, although less marked, behavior is observed for the ^{31}P NMR signals of compounds **1b**,**c** on addition of CSA.

The origin of the extra signals is investigated in the present work by NMR measurements on the separate meso and racemic forms of compounds **1a**, **1b**, and **3** and the meso form of **1c**. The structures of the meso and racemic forms of both compounds **1a** and **3** have been determined previously by X-ray crystallography.[5,6] In the present work, the separate meso and racemic forms of compounds **1b** and the meso form of **1c** have been characterized crystallographically. The individual meso and racemic diastereoisomers of compound **3** have also been investigated by ^{31}P NMR spectroscopy in the presence of CSR and CSA and compared with results for the two meso forms of the doubly bridged macrocyclic-phosphazene compounds **4a**,**b**. It is found that CSRs have little effect on the diastereoisomeric compounds **1a**−**c**,[5] so ^{31}P NMR measurements have been made on the separate meso and racemic forms of compounds **1a** and **1b** (and the meso form of **1c**) in the presence of CSA. The results are compared with analogous NMR measurements with CSA on per-substituted spermine-bridged cyclophosphazene compounds, **2a**,**b**,**d** (X = Ph, NHBu^t, Cl, respectively), and **2c** [X_2 = $O(CH_2)_3O$], which are achiral, and with meso and racemic forms of substituted cyclophosphazenes, **5a**−**d**, which have only one cyclophosphazene ring. Compound **2d** has been synthesized

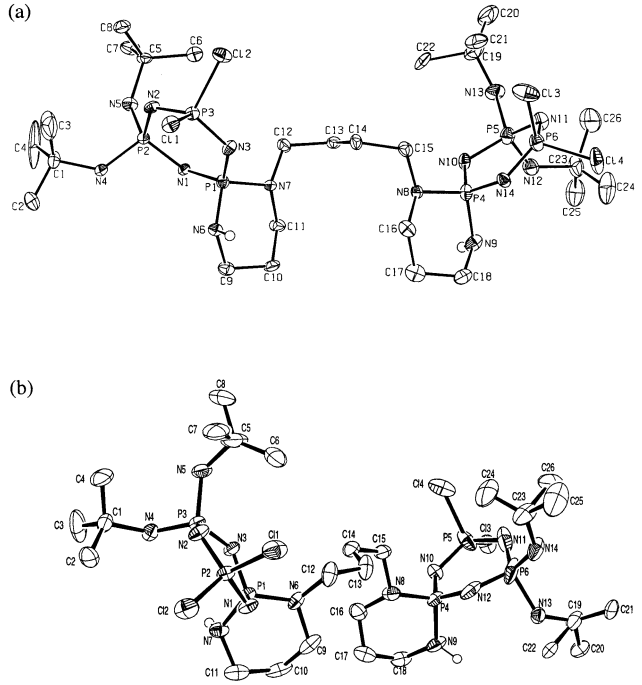

Figure 2. Molecular structures of the (a) meso and (b) racemic forms of the spermine-bridged *gem*-disubstituted cyclotriphosphazatrienes of **1b (**with the disorder in the NHBu^t groups and the hydrogen atoms, except for NH, of the diaminopropane spiro ring omitted for clarity).

and characterized previously,[10] and the synthesis and X-ray crystal structures of the other achiral compounds **2a**−**c** will be published elsewhere.[11] The synthesis and X-ray crystal structures of the meso compounds **5a**[12] and **5b**,**c**[13] have been published. The synthesis of the important racemic compound **5d** and structural characterization by X-ray crystallography are described in this work.

X-ray Crystal Structures of the Meso and Racemic Forms of the Spermine-Bridged Compounds, 1b,c. Figure 2 depicts the molecular structures of (a) the meso and (b) racemic forms of **1b**. The diaminopropane moieties are attached to the cyclotriphosphazatriene groups at atoms P1 and P4, which exhibit differing chirality in the meso structure and the same chirality in the racemic compound. In both compounds, the diaminopropane spiro rings are in chair conformations, while the N_3P_3 rings show considerable deviations from planarity.

The molecular structure of **1c** is depicted in Figure 3. The molecule is meso because the chirality about P1 is *S*, with the center of symmetry inverting this to *R* in the symmetry-generated second part of the molecule. The six-membered spiro ring diaminopropane substituents of the N_3P_3 rings are both in the preferred chair conformation.

X-ray Crystal Structure of the Racemic Compound 5d. The molecular structure of **5d** is shown in Figure 4. It is seen that the ansa macrocyclic moiety is in the cis configuration, so that the anilino and phenoxy substituents are also mutually cis. The macrocycle is found to be in a relatively relaxed crown

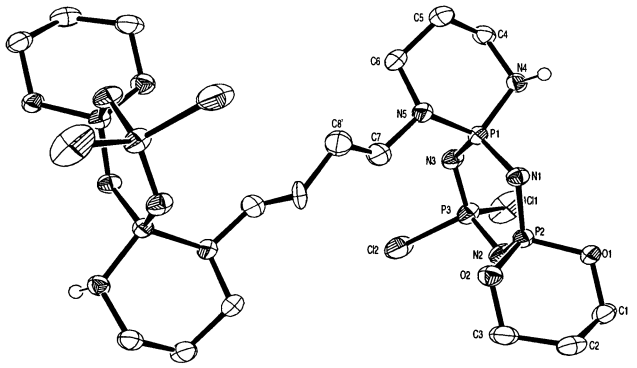

Figure 3. Molecular structure of the meso form of the spermine-bridged *gem*-disubstituted cyclotriphosphazatriene **1c** (with the disorder arising from the inversion center in the middle of the four-membered alkyl bridge omitted for clarity, as well as all of the hydrogen atoms, except for NH).

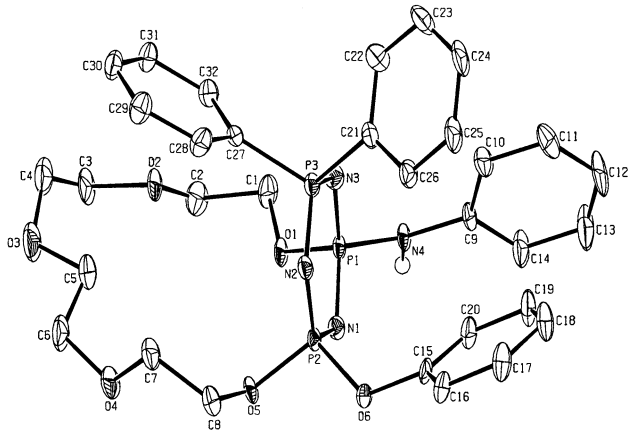

Figure 4. Molecular structure of one enantiomer of the unsymmetrically disubstituted macrocyclic-phosphazene compound **5d** (with hydrogen atoms omitted for clarity, except for NH).

conformation, causing little perturbation to the planarity of the N_3P_3 ring. The cyclophosphazene ring constituents P1 and P2 both exhibit the same chirality, which is the *S* configuration for the absolute structure shown in Figure 4.

Effect of Addition of CSA or CSR on the ^{31}P NMR Spectra of the Isolated Meso and Racemic Forms of Bridged Cyclophosphazene Compounds, 1a,b, 3. Unequivocal assignments of the ^{31}P NMR spectra of the meso and racemic forms of **1b** were made in this work as a result of their chromatographic separation and complete structural characterization by X-ray crystallography, similar to those for **1a** and **3** made previously.[5,6] Unequivocal assignment of the ^{31}P NMR spectra of the meso and racemic forms of **1c** has been made by comparison of the spectrum of the isolated meso form with that of the diastereoisomeric mixture, to which an aliquot of the authentic meso form had been added. The assignments of the ^{31}P NMR spectra for all compounds **1a**−**c**, **3** are summarized in Table 1.

The effects of addition of CSA on the ^{31}P NMR spectra of the meso and racemic forms of compounds **1a** and **1b** (and the meso form of **1c**) were carried out semiquantitatively by titration of a known concentration of CSA into known concentrations of compounds in the same solvent. As expected, it was found that ^{31}P NMR signals of the racemic forms separated into two sets of lines in a 1:1 ratio, with the magnitude of the separation varying for different ^{31}P NMR signals. Unexpectedly, it was

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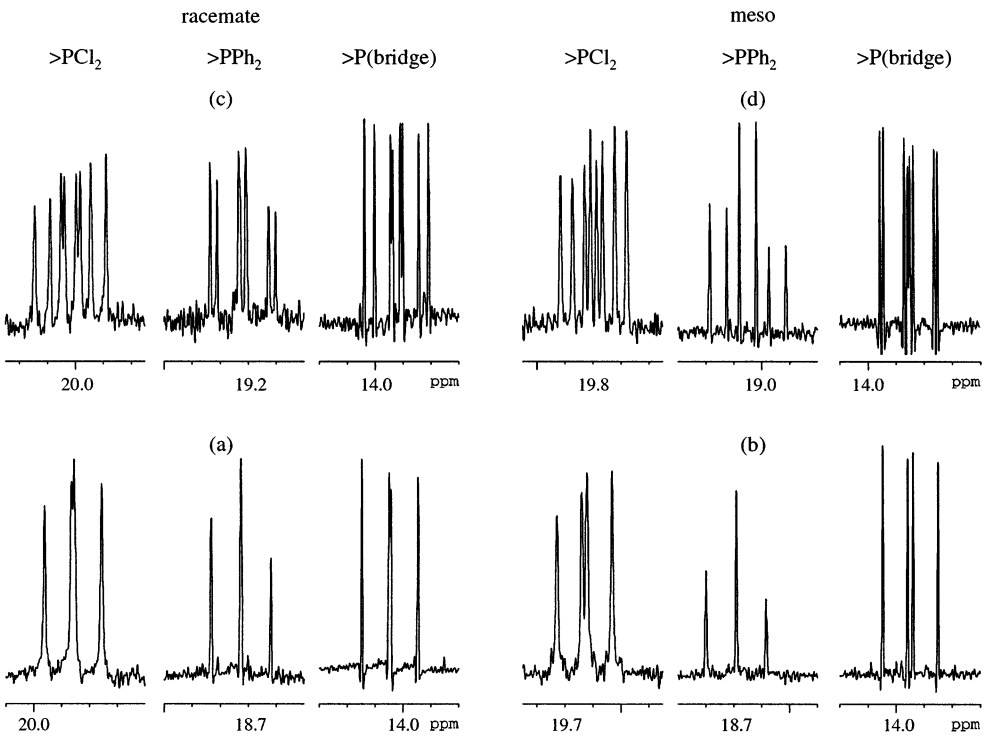

Figure 5. 200 MHz proton-decoupled ^{31}P NMR spectra of (a) the racemic and (b) the meso forms of compound **1a**. Addition of CSA in a ~10:1 mole ratio causes a doubling of signals for both the (c) racemic and the (d) meso forms of **1a**.

Table 1. ^{31}P NMR Parameters of Meso and Racemic Forms of Bridged Cyclophosphazenes[a]

			chemical shifts/ppm				^2J(PP)/Hz		
cpd	solv.	isomer	1	2	3		1,2	1,3	2,3
				(i) Spermine-Bridged Compounds					
			>PCl_2	>P(bridge)	>PX_2	X or X_2			
1a[b]	Tol.	r	19.85	14.05	18.72	phenyl	19.7	21.6	21.0
		m	19.63	13.95	18.70	phenyl	18.1	21.8	22.0
		$\Delta\delta$	0.22	0.10	0.02				
1b[b]	Tol.	r	22.48	14.30	6.88	$NHBu^t$	40.3	50.0	42.0
		m	22.46	14.21	6.86	$NHBu^t$	40.4	50.0	42.1
		$\Delta\delta$	0.02	0.09	0.02				
1c[c]	Chl.	r	25.10	15.45	9.01	$O(CH_2)_3O$	40.5	68.7	63.4
		m	25.00	15.42	8.99	$O(CH_2)_3O$	40.5	68.7	63.4
		$\Delta\delta$	0.10	0.03	0.02				
2a	Chl.			14.58	18.38	phenyl			12.3
2b	Tol.			18.18	10.05	$NHBu^t$			40.2
2c	Chl.			19.77	14.59	$O(CH_2)_3O$			58.0
2d	Chl.			10.39	22.10	Cl			40.5
				(ii) Piperazine-Bridged Compounds					
			>PCl_2	>P(bridge)	>P(OR)Cl				
3[b]	Chl.	r	26.35	14.92	20.35		79.0	58.3	56.3
		m	26.37	14.89	20.40		79.0	58.1	56.3
		$\Delta\delta$	−0.02	0.03	−0.05				
4[d]	Chl.	m_1	27.64	17.01			59.6		
		m_2	26.90	16.59			57.9		
		$\Delta\delta$	0.74	0.42					

[a] 200 MHz ^{31}P NMR measurements in $CDCl_3$ (Chl) or toluene-d_8 (Tol) solutions at 298 K. [b] The meso (m) and racemic (r) forms have been unequivocally assigned as a result of the independent determination of structures by X-ray crystallography. $\Delta\delta = (\delta_r - \delta_m)$. [c] X-ray crystal structure of the meso form enabled assignment to be made by addition of an aliquot of the meso form to a mixture of isomers. $\Delta\delta = (\delta_r - \delta_m)$. [d] The two meso forms (m_1 and m_2) have been unequivocally assigned as a result of the independent determination of structures by X-ray crystallography. $\Delta\delta = (\delta_{m1} - \delta_{m2})$.

found that the ^{31}P NMR signals of the meso form also separated into two sets of lines in a 1:1 ratio, with the magnitude of the separation varying for different ^{31}P NMR signals and for the meso and racemic forms of the same compound. An example of this is shown for compound **1a** in Figure 5.

The ABX spin system of the racemic form of compound **1a** in Figure 5a separates into two sets of signals of equal intensity on addition of CSA (Figure 5c), with the order of the magnitude of the effect on PCl_2 > P(bridge) > PPh_2. The ABX spin system of the meso form of compound **1a** in Figure 5b also separates into two sets of signals of equal intensity on addition of CSA as shown in Figure 5d, but now the order of the magnitude of the effect is PPh_2 > PCl_2 > P(bridge). Although addition of CSA at relatively low concentrations to mixtures of meso and

Table 2. Effect of Addition of CSA or CSR on ^{31}P NMR Chemical Shifts

cpd	solv.	isomer	change in chemical shifts/ppb[a]			separation of signals/ppb[b]		
			(i) CSA with Spermine-Bridged Compounds at 10:1 Mole Ratio[c]					
		X or X_2	$>PCl_2$	>P(bridge)	$>PX_2$	$>PCl_2$	>P(bridge)	$>PX_2$
1a	Tol	r	phenyl	90	−70	285	32	22	18
		m	phenyl	80	−51	175	20	7	32
1b	Tol	r	$NHBu^t$	130	−60	106	0	64	4
		m	$NHBu^t$	80	−5[d]	122	47	55	10
1c	Chl	m	$O(CH_2)_3O$	28	−145	14	27	56	15
2a	Chl		phenyl		−220	1260			
2b	Tol		$NHBu^t$		304	340			
2c	Chl		$O(CH_2)_3O$		−164	−48			
2d	Chl		Cl	37	−21				
			(ii) CSA with Piperazine-Bridged Compounds at 10:1 Mole Ratio					
			$>PCl_2$	>P(bridge)	>P(OR)Cl	$>PCl_2$	>P(bridge)	>P(OR)Cl
3	Chl	r	42	*e*	12	18	*e*	23
		m	43	*e*	11	16	*e*	17
4	Chl	m_1	24	−12				
		m_2	18	−10				
			(iii) CSR with Piperazine-Bridged Compounds at 0.3:1 Mole Ratio					
3	Chl	r	145	540	435	50	190	175
		m	115	440	360	10	65	100
4		m_1	64	118				
		m_2	58	110				

[a] $\Delta\delta = (\delta_{CSA} - \delta_{orig.})$; $\Delta\delta$ positive for high-frequency shifts on addition of CSA or CSR. [b] Absolute value of $|\Delta\delta|$. [c] No effect observed on addition of CSR to these molecules (ref 5). [d] Derived by extrapolation from results at >10:1 mole ratio. [e] Magnitude too small to observe up to a 13:1 mole ratio.

racemic forms of compounds **1a**−**c** did cause the two sets of signals to separate into the expected three groups of lines with relative intensities of 2:1:1,[5] the results summarized in Figure 5 demonstrate that such observations cannot be used to assign the meso and racemic forms unequivocally. Complete assignment depends on knowledge of the relative magnitudes of the effects of addition of CSA for both meso and racemic forms. For example, the relative magnitude of the effect of addition of CSA on the ^{31}P NMR signals of compound **1a** is PCl_2(r) ≈ PPh_2(m) > PCl_2(m) ≈ P(bridge)(r) > PPh_2(r) > P(bridge)(m), so that the first sets of signals to separate into two lines with a 1:1 ratio are those for the racemic form of PCl_2 and the meso form of PPh_2, which would immediately lead to an incorrect assignment of signals. As the relative magnitudes of the effects are quite large for the PPh_2 and PCl_2 groups, these parts of the ^{31}P NMR AMX multiplets of **1a** eventually separate into 16 lines on further addition of CSA, whereas the signals for the P(bridge) group separate into 12 lines (because the effect for the meso form is so small as compared to that for the racemic form).

Similar semiquantitative ^{31}P NMR measurements have been made for the addition of CSA to the separate meso and racemic forms of compounds **1b** and the meso form of **1c**. The results are summarized in Table 2 for the situation where CSA has been added to a 10:1 mole ratio for all compounds. It can be seen that, for each compound **1a**−**c**, there is a similar pattern of changes in chemical shifts on addition of CSA, in that signals of the chiral bridging group move to low frequency and those for the PCl_2 and PX_2 (X ≠ Cl) groups move to high frequency. The changes of chemical shift of ^{31}P NMR signals on titration with CSA indicate that the CSA complexes to each of the molecules and that one site of binding is likely to be the P(bridge) moiety in each of the molecules **1a**−**c**. There are large differences in the effect of CSA on the PCl_2 and PX_2 (X ≠ Cl) signals in the series of compounds **1a**−**c**, probably reflecting differences in complexation of CSA with molecules containing different substituents (i.e., X = phenyl, $NHBu^t$ and $X_2 = OCH_2$-CH_2CH_2O groups). The results in Table 2 also show that, at a 10:1 mole ratio of CSA:compound, there is a differential effect on the chemical shift separation of meso and racemic forms for each compound **1a**,**b**, which is also likely to reflect varying contributions to the equilibrium of different complexed forms for the different molecules.

Similar behavior is observed for the meso and racemic forms of compound **3**, and the results are summarized in Table 2. In this case, it was found that addition of either CSR or CSA causes a doubling of signals of the separate meso and racemic forms of compound **3**, the effect for CSR being much greater than that for CSA as shown by the results in Table 2.

Discussion

Explanation of the Doubling of ^{31}P NMR Signals of the Meso Forms of Compounds (1a−c, 3) on Addition of CSA or CSR. The accepted explanation of the effect of CSA and CSR on the NMR spectra of enantiomers is that there is an equilibrium in solution of complexes of chiral ligand L and chiral molecule M and that all free and complexed forms are in fast exchange on the NMR time scale.[1,2]

Let the racemic mixture of a chiral molecule be represented as $M_R + M_S$, the meso form of a molecule as M_R^S and the chiral ligand as L_R.

For the racemate in solution, there is an equilibrium mixture of complexes represented in eq 1.

$$M_R + M_S + L_R \rightleftharpoons M_R{\cdot}L_R + M_S{\cdot}L_R \qquad (1)$$

The complexes $M_R{\cdot}L_R$ and $M_S{\cdot}L_R$ are diastereoisomers and are expected to have different NMR chemical shifts. The observed NMR spectrum is the weighted average of the chemical shifts of the molecule and its complexes in solution, and so, on titration with a solution of L_R, the spectrum of M will separate into two signals as the relative proportions of the $M_R{\cdot}L_R$ and $M_S{\cdot}L_R$ diastereoisomers increase.

For the meso form in solution, on the other hand, the equilibrium mixture represented in eq 2 does not form diastereoisomers, and the weighted average chemical shift gives only one set of NMR signals.

$$M_R^S + L_R \rightleftharpoons M_R^S \cdot L_R \quad (2)$$

Let the symmetrically substituted spermine-bridged cyclophosphazenes **1a**−**c** be represented as M−M. Each P(bridge) group is stereogenic, and so the chirality of the bridged molecules may be represented as racemate, $M_R-M_R + M_S-M_S$, or meso, $M_R-M_S = M_S-M_R$. On addition of CSR or CSA (L_R), it is expected that the chiral agent can complex with either or both cyclophosphazene rings, that the NMR signal is a local reporter of each cyclophosphazene ring, and that the observed NMR chemical shifts are the weighted averages of all complexed and uncomplexed forms. The complexes expected for the racemic forms are summarized in eq 3

$$M_R-M_R + L_R \rightleftharpoons L_R\cdot M_R-M_R + M_R-M_R\cdot L_R + L_R\cdot M_R-M_R\cdot L_R \quad (3a)$$

$$M_S-M_S + L_R \rightleftharpoons L_R\cdot M_S-M_S + M_S-M_S\cdot L_R + L_R\cdot M_S-M_S\cdot L_R \quad (3b)$$

If $f_{(RR)i}$ and $f_{(SS)i}$ represent the fractions in the *i*th state (free or complexed) of M_R-M_R and M_S-M_S enantiomers, respectively, the weighted average chemical shifts of all of the $M_R\cdot L_R$ forms in eq 3a depend on $\sum f_{(RR)i} \times \delta(M_R\cdot L_R)_i$, and the weighted average chemical shifts of all of the $M_S\cdot L_R$ forms in eq 3b depend on $\sum f_{(SS)i} \times \delta(M_S\cdot L_R)_i$. Even when $f_{(RR)i}$ and $f_{(SS)i}$ are equal, it is expected that the diastereoisomeric chemical shifts of $M_R\cdot L_R$ and $M_S\cdot L_R$ are different and so the NMR signals of the components of the racemic mixtures are different.

The meso forms of the bridged cyclophosphazenes **1a**−**c** have equal proportions of the linked M_R and M_S moieties, and complexation with the chiral ligand L_R is considered in eq 4

$$M_R-M_S + L_R \rightleftharpoons L_R\cdot M_R-M_S + M_R-M_S\cdot L_R + L_R\cdot M_R-M_S\cdot L_R \quad (4)$$

Whatever the relative proportions of the complexed forms of L_R with the meso isomer, complexation with the M_R part of the molecule gives chemical shifts characteristic of the $M_R\cdot L_R$ form, and complexation with the M_S part of the molecule gives chemical shifts characteristic of the $M_S\cdot L_R$ form. In the meso form of compounds **1a**−**c**, the two P(bridge) groups are chiral, where M_R is separated from M_S by a long achiral spacer of seven bonds, and it is assumed that L_R complexes independently with each cyclophosphazene ring. The differences in the NMR signals of the meso form on addition of CSR or CSA occur because the chemical shifts of $M_R\cdot L_R$ and $M_S\cdot L_R$ are different. Similar behavior is expected for the meso form of compound **3**, where the M_R and M_S moieties of the bridge are now separated by five bonds, and complexation with either CSR or CSA causes doubling of all ^{31}P NMR signals.

Test of Analysis with Achiral Analogues of Spermine-Bridged Cyclophosphazenes, 2a−**d.** To test the explanation developed for meso compounds, a series of per-substituted spermine-bridged cyclophosphazenes (compounds **2a**−**d**) has been synthesized. Although these molecules have two cyclophosphazene rings separated by the same achiral spacer as in compounds **1a**−**c**, they are not chiral because of the symmetry properties of each substituted cyclophosphazene ring. On titration with CSA of a solution of each compound **2a**−**d**, the ^{31}P NMR chemical shifts of the P(bridge) and PX_2 groups changed progressively, indicating complexation of CSA with the cyclophosphazene derivatives (results in Table 2), but, as expected, no separation into two groups of lines occurred even on addition of CSA up to a mole ratio CSA:**2a**−**d** of at least 20:1. If M−M represents the achiral bridged molecule, then it can be seen in eq 5 that complexation with CSA (L_R) causes the same chemical shift effect on both parts of the molecule and hence, as observed, there is no doubling of signals.

$$M-M + L_R \rightleftharpoons L_R\cdot M-M + M-M\cdot L_R + L_R\cdot M-M\cdot L_R \quad (5)$$

Test of Analysis with the Two Meso Forms of Double-Bridged Cyclophosphazenes, 4a,b. The syn-meso form of the double-bridged cyclophosphazene, **4a**, results from the reaction of piperazine with the meso form of compound **3**, and the configurations of the two P(bridge) groups are *R*:*S*, whereas the anti-meso isomer of **4b** results from the racemic form of **3**, and the configurations of the two P(bridge) groups are *R*:*R* and *S*:*S*.[6] Although compounds **4a** and **4b** have the same piperazine bridge as that of compound **3**, no splitting of signals was observed for either **4a** or **4b** on addition of CSR up to a mole ratio of 1.3:1 or addition of CSA up to a mole ratio of 27:1. These observations can be explained by consideration of the equilibrium complexation of chiral ligand with the molecules.

Each macrocyclic-phosphazene moiety in **4a** and **4b** has the same two stereogenic P(OR)(piperazine) groups, which are always *S* and *R*, and so may be represented as M_R^S. Hence, to account for the fact that in **4a** both of the bridges are *R*:*S*, the double-bridged molecule may be represented $M_R^S{=}M_S^R$ (having a plane of symmetry), while in **4b** the configurations of the bridges are *R*:*R* and *S*:*S*, that is, $M_R^S{=}M_R^S$ (center of symmetry), which readily reflects the symmetry properties of the two meso compounds. Addition of CSA/CSR is expected to have the same effect on the ^{31}P NMR signals of each macrocyclic-phosphazene moiety, as shown in eq 6, and hence no doubling of signals is expected, as was observed.

$$M_R^S{=}M_S^R + L_R \rightleftharpoons L_R\cdot M_R^S{=}M_S^R + M_R^S{=}M_S^R\cdot L_R + L_R\cdot M_R^S{=}M_S^R\cdot L_R \quad (6a)$$

$$M_R^S{=}M_R^S + L_R \rightleftharpoons L_R\cdot M_R^S{=}M_R^S + M_R^S{=}M_R^S\cdot L_R + L_R\cdot M_R^S{=}M_R^S\cdot L_R \quad (6b)$$

Test of Analysis with Meso and Racemic Forms of Macrocyclic-cyclophosphazenes Derivatives, 5a−**d.** The model is also tested on meso and racemic forms of cyclophosphazene derivatives, which have only one substituted cyclophosphazene ring for complexation with CSA or CSR. The molecules **5a**−**d** are macrocyclic-phosphazene derivatives, and so they complex with both CSA and CSR. It is found that the ^{31}P NMR signals of the racemic compound, **5d**, split into two signals of equal intensity on addition of either CSA or CSR as predicted by eq 1, whereas the ^{31}P NMR signals of the meso compounds, **5a**−**c**, do not split as predicted by eq 2. Hence, addition of CSA or CSR to the meso form of molecules containing one cyclophos-

phazene ring behaves as expected for meso compounds, in general.[1,2] A similar difference in NMR behavior between meso and racemic forms of cyclophosphazene derivatives had previously been observed on addition of CSR to a mixture of mono-*n*-propylamino (racemic) and di-*n*-propylamino (meso) derivatives of macrocyclic-cyclophosphazene compounds,[6] although in this case there was no X-ray crystallographic evidence to prove the structures and stereogenicity of the compounds.

Conclusions

It is found that addition of chiral shift reagent or chiral solvating agent to separate meso and racemic forms of some diastereoisomeric single-bridged cyclophosphazene compounds causes doubling of ^{31}P NMR signals for both isomers. The anomalous NMR behavior on addition of CSR/CSA is only found for meso forms of cyclophosphazene compounds, where the two nearest stereogenic centers are separated by long achiral spacers, for example, five bonds (compound **3**) or seven bonds (compounds **1a**−**c**). The unexpected behavior is explained by consideration of the equilibrium complexation of a chiral ligand with such meso compounds. The results show that the stereogenicity of the meso and racemic forms of diastereoisomeric molecules in solution cannot be characterized unequivocally by NMR measurements on addition of either CSR or CSA, unless the isolated forms are separately characterized. It will be of interest to investigate the necessary and sufficient conditions to observe this anomalous NMR behavior for other meso compounds not based on cyclophosphazenes.

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Supporting Information Available: All experimental details (materials, methods, X-ray data, and synthesis of **5d**) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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