Influence of Strong Transannular N → P Interaction on Acidity of Cyclenphosphine Sulfide

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The acid-base behavior of cyclenphosphine sulfide (cyclenPS) is appreciably different from that of cyclamphosphine sulfide (cyclamPS). The cyclenPS shows five acid functionalities compared to four for cyclamPS. The fifth acidic group in cyclenPS corresponds to the formation of a stable amidure in aqueous solution ($pK_{a_5} = 12.3$). This behavior is due to the strong transannular N → P interaction. The deprotonation sequences were established by ^{31}P-NMR and confirmed by modelling of cyclenPS.

Introduction. – In recent years, much work has been devoted to the synthesis of polyazamacrocycles with pendant arms. The problem of selective mono-*N*-alkylation, therefore, remains an interesting challenge. Recently, we have proposed a stoichiometric triprotection of cyclen (= 1,4,7,10-tetraazacyclododecane) and cyclam (= 1,4,8,11-tetraazacyclotetradecane) involving either a phosphoryl or a thiophosphoryl group [1–3]. In comparison with that of its larger homologs, the behavior of the triprotected cyclen is unexpected. Indeed, in addition to mono-*N*-functionalization, either a dialkylation at N(2) and N(4) with the PO group, or a *N*(4)- or *S*-alkylation with the PS group is also observed.

This behavior can be interpreted as the result of a strong interaction between the free doublet of the N-atom of the secondary amine and the P-atom which does not occur with cyclamPS.

In this paper, we verify the effect of this N → P interaction on the acidity constants of the thiophosphorylated derivatives, namely cyclamphosphine sulfide (cyclamPS) and cyclenphosphine sulfide (cyclenPS) on the basis of the ^{31}P-NMR chemical-shifts results. These results are supported by a modelling study of the ionic and neutral forms of cyclenPS.

Results and Discussion. – *Protometric and NMR Studies.* The values of the acidity constants of cyclamPS and cyclenPS were calculated and refined with the computer program PROTAF [4][5]. This program is based on a least-squares method which minimizes the weighted sum of the residues of the experimental variables, namely volume of KOH added and pH measured.

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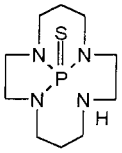
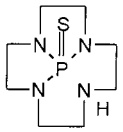


CyclamPS

L_aH



CyclenPS

L_eH

The weighted sum is defined by the expression:

$$S = \sum_i [W_{V_i} R_{V_i}^2 + W_{\mathrm{ph}_i} R_{\mathrm{pH}_i}^2]$$

with the residues $R_{V_i} = V_{i\,\mathrm{exp}} - V_{i\,\mathrm{refined}}$ and $R_{\mathrm{pH}_i} = \mathrm{pH}_{i\,\mathrm{exp}} - \mathrm{pH}_{i\,\mathrm{refined}}$, and where W_{V_i} and W_{pH_i} are the weighting linked to the accuracy of the volumes and of the pH measurements.

As well as the acidity constants, it is simultaneously possible to refine the other parameters of the titrations, such as ionic product of H_2O and the concentrations of the studied solutions. The results obtained are presented in the *Table*.

Table. *Acidity Constants of CyclamPS and CyclenPS*

	$LH_3^{2+} \rightleftharpoons LH_2^+ + H^+$ pK_{a_3}	$LH_2^+ \rightleftharpoons LH + H^+$ pK_{a_4}	$LH \rightleftharpoons L^- + H^+$ pK_{a_5}
CyclamPS (**L_aH**)	< 1.5	9.65 (0.03)[a])	[b])
CyclenPS (**L_eH**)	1.10 (0.08)[a])	9.90 (0.04)[a])	12.3 (0.2)[a])

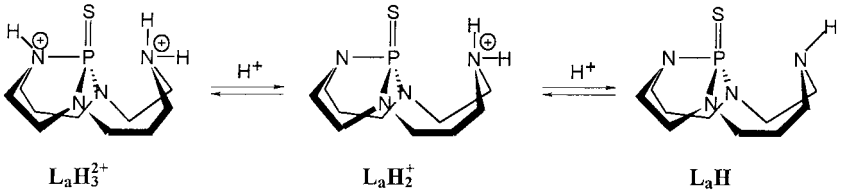
[a]) Values in parentheses refer to the estimated standard deviations (95% confidence).
[b]) Unobservable acidity in aqueous solution.

The protometric measurements were carried out over a large pH range between 2 and 12. The titrated solutions contained an excess of HNO_3 which allowed a partial reprotonation of the ligands cyclamPS and cyclenPS, leading to the cationic forms $LH_n^{(n-1)+}$.

In the experimental conditions that we used, the first two acidity constants of the ligands (pK_{a_1} and pK_{a_2}), which correspond to the pairs LH_5^{4+}/LH_4^{3+} and LH_4^{3+}/LH_3^{2+}, respectively, could not be determined because: *1*) these two pK_a values are very low (probably lower than 1), thus the concentration of the protonated forms LH_5^{4+} and LH_4^{3+} remain negligible in solution for pH values greater than 2; and *2*) the values of the first three acidity constants are undoubtedly very similar, which does not allow precise determination of all these values. Therefore, we obtained only the pK_{a_3} values.

CyclamPS. According to the results obtained from ^{31}P-NMR spectroscopy (*vide infra*), the value $pK_{a_4} = 9.65$ is attributed to the reprotonation of the N-atom N(4) not bonded to the P-atom, which leads to the formation of the $L_aH_2^+$ species (*Scheme 1*). In very acidic medium, only the protonation of one of the three other N-atoms is observed ($pK_{a_3} < 1.5$), probably the axial N-atom, known to be more basic than the equatorial N-atoms [6]. In addition to the reasons previously given, the slow decomposition of

Scheme 1



cyclamPS in very acidic medium is another factor which does not allow a precise determination of pK_{a_3}.

The ^{31}P-NMR chemical shift observed for cyclamPS is typically the same as the shift of a tetracoordinated P-atom (91 ppm), and remains almost constant across the pH range (85 ppm in acidic medium, 81.6 ppm in basic medium). The position of the $\tilde{\nu}$(NH) band in the IR spectrum (3330 cm^{-1}), and the exclusive alkylation on this secondary N-atom in the presence of an electrophilic compound, prevent the possibility of an N → P interaction in cyclamPS. The secondary amine functional group can, therefore, be considered as independent from the remaining of the molecule.

Taken as a whole, these results enable us to propose for cyclamPS the deprotonation sequence shown in *Scheme 1*.

CyclenPS. The acid-base behavior of cyclenPS is appreciably different from that of cyclamPS in that three as opposed to two acidity constants could be determined. Indeed, the pK_{a_5} constant corresponds to the formation of the anionic L^- species not observed with cyclamPS.

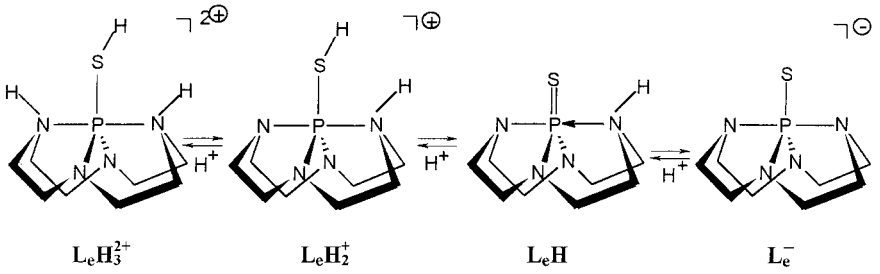
The ^{31}P-NMR spectroscopy also reveals a different behavior from that observed with cyclamPS. Indeed, cyclenPS shows in ^{31}P-NMR a chemical shift of 31.5 ppm in $CDCl_3$ (8.5 ppm in H_2O), intermediate between the shift of a pentacoordinated P-atom and that of a tetracoordinated P-atom engaged in a rather constrained cyclic system [7]. This behavior is characteristic of a strong N → P interaction, which is known to be favored in eight-membered rings, and which leads to a strong increase of the acidity of the corresponding N-atom. The acidity constant then becomes measurable in aqueous solution ($pK_{a_5} = 12.3$).

The evolution of the ^{31}P-NMR chemical shift as a function of the pH is unexpected. In acidic medium, an important shift towards strong fields is observed (– 12.5 ppm). Moreover, the anion chemical shift, obtained through the action of a strong base, is – 51 ppm [3]. These two values are in agreement with a pentacoordinate geometry of the P-atom, for the protonated form as well as for the anionic form.

In HCl solutions, the ^{13}C-NMR spectrum of the protonated form presents two *doublets* at 44.1 ppm (J(P,C) = 8.51 Hz) and at 47 ppm (J(P,C) = 5.5 Hz). This indicates the existence of, on the one hand, a protonation of the S-atom and, on the other hand, a quick exchange that makes the C-atoms of the ring become equivalent two by two.

The anionic form presents only one ^{13}C-NMR chemical shift ($\delta = 44.5$ ppm, J(P,C) = 9.2 Hz), which was interpreted as a quick pseudorotation that makes all the C-atoms of the ring become equivalent [8]. These results together allow us to propose, for cyclenPS, the deprotonation sequence shown in *Scheme 2*.

Scheme 2

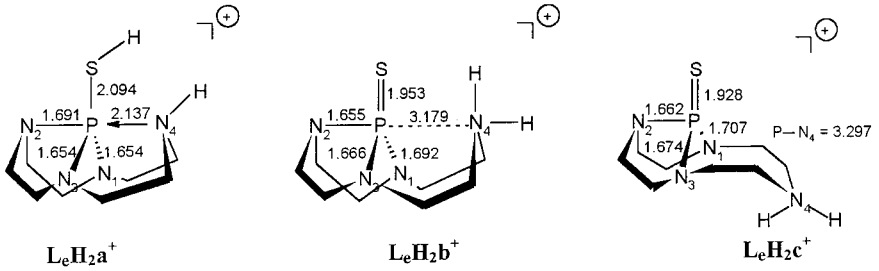


Modelling. To support the NMR findings, we modelled the structures L_eH, $L_eH_2^+$, and L_e^-. Geometries were optimized, and formation energies were computed in gas phase according to the HF/6-31G** formalism, which takes into account the electronic delocalization. The geometric parameters optimized for cyclenPS in its neutral form, **L_eH** (*Fig. 1*), evidence a local pseudo-tetrahedral geometry around the P-atom. Both N-atoms N(1) and N(3) have a quasi-sp^2 geometry, whereas N(2) and N(4) are held in a sp^3 configuration. This is in agreement with the basicity difference measured between nitrogenous sites [6], since, for the equatorial N-atoms N(1) and N(3), there is a retrodonation $p\pi \rightarrow d\pi$ from the doublet of these N-atoms to the P-atom. Moreover, the location of the atom N(4) from the P-atom induces an interaction between its doublet and the P-atom, given that the calculated P–N(4) distance of 3.027 Å is very similar to that determined by X-ray crystallography for thioprophosphatranes [9].

Fig. 1. *Geometrical parameters calculated in HF/6-31G** for cyclenPS* (**L_eH**) *and its anion* **L_e^-** (bond lengths in Å)

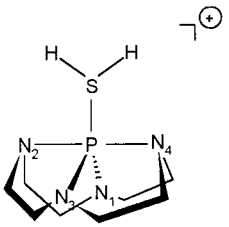
The formation of amidure anion L_e^- was simulated from L_eH by the deprotonation of the secondary amine (*Scheme 2*). The L_e^- anion is characterized by a pentacoordinated P-atom and exhibits (*Fig. 1*) two bonds, P–N(2) and P–N(4), of similar lengths (1.715 and 1.732 Å, resp.) while the distances P–N(1) and P–N(3) are identical (1.830 Å). Moreover, the calculated P–S bond length (2.034 Å) is intermediate between that of a double and that of a single bond. Therefore, we can conclude that the electrons on the S–P–N chain are delocalized, with an increase of electron density around the P-atom, compatible with the strong shielding of the associated ^{31}P-NMR signal.

Finally, the different isomers of the cationic form $L_eH_2^+$ were examined (*Fig. 2*).



$L_eH_2a^+$ $L_eH_2b^+$ $L_eH_2c^+$

$E = -1269.312572$ Ha $E = -1269.295012$ Ha $E = -1269.300018$ Ha



$L_eH_2d^+$

Fig. 2. *Geometrical parameters calculated for protonated derivatives* $\mathbf{L_eH_2^+}$ *of cyclenPS* (bond lengths in Å)

The $L_eH_2a^+$ isomer presents around the P-atom a trigonal bipyramidal geometry with two identical $P-N_{equatorial}$ bonds. The calculated distance P–N(4) of 2.137 Å is shorter than that optimized in the neutral form $\mathbf{L_eH}$ (3.027 Å). For the $\mathbf{L_eH_2b^+}$ and $\mathbf{L_eH_2c^+}$ forms, protonation on the secondary N-atom makes it impossible for this N-atom and the P-atom to interact. The calculated energy for these two isomers shows that they are less stable than the $\mathbf{L_eH_2a^+}$ isomer ($\Delta E_{a-b} = 32.93\ kJ \cdot mol^{-1}$).

Finally, the calculated geometry for $\mathbf{L_eH_2d^+}$ indicates that this compound would not be stable and would sustain an heterolytic breaking of the P–S bond. This result may be related to the slow hydrolysis of cyclenPS to cyclenPO, *via* a cyclenphosphonium with H_2S release, observed in very acidic medium. Thus, the calculation confirms protonation of the S-atom for the $\mathbf{L_eH_2^+}$ **cation.**

Conclusion. – Protometric study established the exceptional behavior of cyclenPS whose secondary amine functional group can be deprotonated in basic medium. The protonation of the S-atom of this molecule is also unexpected. In contrast to cyclamPS, the functional groups NH and thiophosphoryl are interdependent, which may be related to the observation that cyclenPS undergoes a *S*- or *N*-alkylation depending upon the electrophile [3]. The particular behavior of cyclenPS may be explained by the strong transannular N → P interaction.

Experimental Part

General. IR Spectra: *Bomem Michelson 100* spectrophotometer. ^{31}P-NMR Spectra: *Bruker AC 300* spectrometer (121.49 MHz); δ in ppm downfield from external 85% H_3PO_4.

Synthesis. Cyclamphosphine sulfide ($\mathbf{L_aH}$) and cyclenphosphine sulfide ($\mathbf{L_eH}$) were prepared by published procedures [3].

Protometric measurement. All chemicals used were of anal. grade. HNO_3 and KOH were purchased from *Prolabo*. KNO_3 was purchased from *Fluka*. All measurements were performed at an ionic strength adjusted to 1 with KNO_3 in a thermoregulated cell at $20.0 \pm 0.1°$, under N_2 to prevent absorption of CO_2.

The measurement assembly included a microprocessor burette (*Metrohm* Dosimat 665) and a pH meter (*Metrohm 713*) linked to a PC computer. The complete automation of the titrations was achived with software developed in the GRECI laboratory. This software enabled us in particular to choose different addition increment volumes and to fix a stability criterion for pH measurements, as well as the time interval during which this criterion must be respected.

Solns. of cyclamPS and cyclenPS in the concentration range 5×10^{-4} to 3×10^{-3} M were titrated with 0.1M KOH soln. To facilitate determination of the stronger acidities of these two ligands, an amount of HNO_3 was initially added to all solns. (HNO_3/ligand ratios ranging from 3 to 5).

Computation Procedure. Molecular modelling of $\mathbf{L_eH}$, $\mathbf{L_eHa^+}$, $\mathbf{L_eHb^+}$, $\mathbf{L_eHc^+}$, and L_e^- was accomplished with the program SYBYL (TAFF force field) on a *Silicon Graphics* station [10]. The charges on the atoms in the calculation were generated by SYBYL according to the *Gasteiger-Hückel* method. Trial structures of the various conformers of the compounds were generated, and a conformational search was made to find the global minimum of each surface. *Ab initio* calculation was then performed on the previous minima with the Gaussian 94 software package [11]. Geometries were fully optimized without symmetry constraint at the HF level with a 6-31G** basis set and the minima were characterized by the number of negative eigenvalues (none) of the *Hessian* matrix.

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