N^1,N^7-Dialkylation of cyclenphosphine oxide hydrate

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According to experimental conditions, either selective mono *N*-alkylation or N^1,N^7-dialkylation of cyclenphosphine oxide is effected.

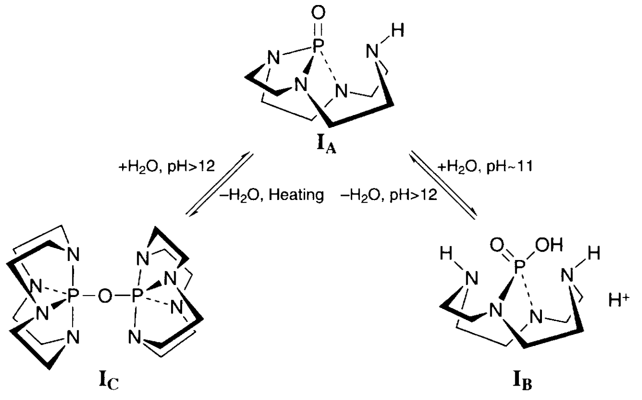
Over the past two decades numerous works have been devoted to the synthesis of polyazamacrocyclic compounds with pendant arms.[1] Recently we have proposed a stoichiometric easy-to-run triprotection of a series of tetraazamacrocycles involving a phosphoryl group. Cyclen was selectively mono *N*-alkylated *via* the reaction of its phosphine oxide with electrophiles and acidic removal of the phosphoryl protecting group.[2] Cyclenphosphine oxide was previously studied by Richman;[3] structure $\mathbf{I}_\mathrm{A}$ (Scheme 1) was proposed for this product on the basis of its spectroscopic data: the free N–H stretching band at 3330 cm^{-1} observed in the IR spectrum and the four distinct carbons (^{13}C NMR, $CDCl_3$) variously coupled with the phosphorous atom at low temperature are consistent with this hypothesis. At higher temperatures this pattern changes to a doublet, indicating a rapid exchange of all the carbon sites probably through a pentacoordinated intermediate.

As observed by Richman,[3] cyclenphosphine oxide is a very hygroscopic material. When exposed to atmospheric moisture, fast addition of water occurs leading to a monohydrate as supported by elemental analysis.†

We report here the unexpected properties of cyclen phosphine oxide in the presence of water.

Typically, cyclenphosphine oxide is prepared by transamination of $P(NMe_2)_3$ with cyclen, oxidation of the resulting P^{III} macrocycle with CCl_4 to give the corresponding phosphonium salt which is finally hydrolysed with aqueous NaOH.[2] The crude extract consists of three compounds in various amounts as shown by ^{31}P NMR ($CDCl_3$): $\mathbf{I}_\mathrm{A}$: δ −8; $\mathbf{I}_\mathrm{B}$: δ −20 and $\mathbf{I}_\mathrm{C}$: δ −30. Compound $\mathbf{I}_\mathrm{C}$ can be readily separated by crystallization in a 1 : 1 Et_2O–CH_2Cl_2 mixture, afterwards, $\mathbf{I}_\mathrm{A}$ and $\mathbf{I}_\mathrm{B}$ are easily isolated and characterized.

^{13}C, ^{31}P and ^{1}H NMR data enabled us to identify $\mathbf{I}_\mathrm{A}$‡ as the well known cyclenphosphine oxide (Scheme 1). However, we observed that its hydrate, in solid state, was slowly converted into $\mathbf{I}_\mathrm{B}$ at room temperature.



Scheme 1

In $CDCl_3$, $\mathbf{I}_\mathrm{B}$ exhibited two signals in the ^{13}C NMR spectrum: at δ 44.1 (broad) and 43.2 (doublet, *J* 11 Hz); its ^{1}H spectrum shows four poorly resolved multiplets and a broad signal at δ 7 attributed to acidic hydrogens. Futhermore, a mild dehydratation by azeotropic distillation (toluene) regenerates $\mathbf{I}_\mathrm{A}$. In addition, reaction of $\mathbf{I}_\mathrm{B}$ with 2 equiv. of an electrophile in DMF in the presence of sodium carbonate as proton scavenger, leads in high yields, after acidic hydrolysis, to N^1, N^7-dialkylated cyclen. In all cases ^{31}P NMR signals of the intermediates takes place near δ −20 (Table 1).

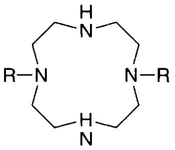
All these data suggest the structure for $\mathbf{I}_\mathrm{B}$ as depicted in Scheme 1 in non-aqueous medium, probably in a zwitterionic form. This product corresponds to the selective opening of the P–N bond opposite to the free secondary amine in $\mathbf{I}_\mathrm{A}$. The high selectivity of this process can find its explanation in the weakening of the bond due to the strong transannular P ← N interaction[3] also observed for the thiophosphoryl analogue of cyclenphosphine oxide.[4]

In D_2O, ^{31}P NMR spectroscopy indicated a rapid and strongly pH dependent equilibrium between $\mathbf{I}_\mathrm{A}$ and $\mathbf{I}_\mathrm{B}$: $\mathbf{I}_\mathrm{A}$ was predominant above pH = 12. On decreasing the pH, the ^{31}P NMR signal shifts are consistent with a titration curve corresponding to a rapid conversion of $\mathbf{I}_\mathrm{A}$ into $\mathbf{I}_\mathrm{B}$ associated to a proton exchange, and below pH = 11 $\mathbf{I}_\mathrm{B}$ dominates. This pH dependence suggests a protonated form of $\mathbf{I}_\mathrm{B}$ in water, stabilized by intramolecular hydrogen bonding.

Compound $\mathbf{I}_\mathrm{C}$‡ was obtained pure when $\mathbf{I}_\mathrm{A}$ (or $\mathbf{I}_\mathrm{B}$) was extensively dehydrated by heating at 150 °C. Two doublets at δ 43.1 (J_{PC} 5 Hz) and 42.1 J_{PC} 11 Hz) were observed in ^{13}C NMR ($CDCl_3$) and its ^{1}H NMR spectrum ($CDCl_3$) showed four well resolved multiplets at δ 2.85, 3.05, 3.35 and 3.65 for four anisochronous hydrogen localized on two different carbons of the macrocycle. The ^{31}P NMR signal at δ −30 was in agreement with a pentacoordinated phosphorus,[5,6] as expected for $\mathbf{I}_\mathrm{C}$ (Scheme 1).

Treatment with aqueous sodium carbonate at room temperature slowly converted $\mathbf{I}_\mathrm{C}$ into $\mathbf{I}_\mathrm{B}$ probably *via* $\mathbf{I}_\mathrm{A}$, since in more basic medium (sodium hydroxide, pH > 12) $\mathbf{I}_\mathrm{A}$ is regenerated. The dimeric form $\mathbf{I}_\mathrm{C}$ is also a side product from the hydrolysis of the phosphonium salt and for this reason it can be found in various amounts in the crude reaction mixture.

Table 1 N^1,N^7-Disubstitution of 1,4,7,10-tetraazacyclododecane

Alkylating agent	Stoichiometry	End product	Yield (%)	δ_P (intermediate)
				
MeI	2	R = Me	80	−21
$PhCH_2Br$	2	R = CH_2Ph	95	−16
$HC{\equiv}CCH_2Cl$	2	R = $CH_2C{\equiv}CH$	95	−19
PrBr	2	R = Pr	80	−17

To sum up, cyclenphosphine oxide can be reversively hydrated or dehydrated, according to experimental conditions (Scheme 1). Therefore, $\mathbf{I_A}$ is the only form observed when hydrolysis of the phosphonium salt is performed at pH > 12.

Moreover, semi-empirical calculations (AM1 formalism), in the gas phase, are in agreement with the spontaneous conversion of cyclenphosphine oxide hydrate into $\mathbf{I_B}$, since $\mathbf{I_B}$ is more stable than $\mathbf{I_A}H_2O$(ΔE = 12 kcal mol^{-1}, 1 cal = 4.184 J).

This behaviour is not observed for higher homologues of $\mathbf{I_A}$, like cyclamphosphine oxide, with larger fused rings for which no transannular P ← N interaction is observed.[7]

This study shows that cyclenphosphine oxide behaves differently according to the experimental conditions: its mono *N*-alkylation requires strictly anhydrous reagents and medium,[2] but its hydrate, in presence of 2 equiv. of an electrophile, is easily N^1, N^7-dialkylated. This method constitutes a new route to this class of compounds.[8–10]

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Footnotes

† Elemental analysis: Anal. calc. for $C_8H_{17}N_4PO$, H_2O: C, 41.02; H, 8.11; N, 23.93; P, 13.25; O, 13.67. Found: C, 41.56; H, 8.71; N, 23.99; P, 12.18; O, 13.56%. MS *m*/*z* (%): 234 (M$^+$, 2.5), 216 (68) and 199 (100).

‡ Compounds $\mathbf{I_A}$, $\mathbf{I_B}$, $\mathbf{I_C}$ were characterized by ^{1}H NMR (300 MHz, $CDCl_3$), ^{13}C NMR (75.45 MHz, $CDCl_3$) and ^{31}P NMR (40.26 MHz, $CDCl_3$).

References

1 E. Kimura, *Tetrahedron*, 1992, **48**, 6175.

2 A. Filali, J. J. Yaouanc and H. Handel, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 560.

3 J. E. Richman and J. J. Kubale, *J. Am. Chem. Soc.*, 1983, **105**, 749.

4 N. Oget, F. Chuburu, J. J. Yaouanc and H. Handel, *Tetrahedron*, 1996, **52**, 2995.

5 J. E. Richman, R. O. Day and R. R. Holmes, *J. Am. Chem. Soc.*, 1980, **102**, 3955.

6 J. E. Richman, R. O. Day and R. R. Holmes, *Inorg. Chem.*, 1981, **20**, 3378.

7 J. E. Richman, R. B. Flay and O. D. Gupta, *ACS. Symp. Ser.*, 1981, **171**, 271.

8 M. Ciampolini, M. Micheloni, N. Nardi, P. Paoletti, P. Dapporto and F. Zanobini, *J. Chem. Soc., Dalton Trans.*, 1984, 1357; P. L. Anelli, M. Murru, F. Uggeri and M. Virtuani, *J. Chem. Soc., Chem. Commun.*, 1991, 1317.

9 A. Roignant, I. Gardinier, H. Bernard, J. J. Yaouanc and H. Handel, *J. Chem. Soc., Chem. Commun.*, 1995, 1233.

10 V. Patinec, J. J. Yaouanc, H. Handel, J. C. Clement and H. des Abbayes, *Inorg. Chim. Acta*, 1994, **220**, 347; V. Patinec, I. Gardinier, J. J. Yaouanc, J. C. Clement, H. Handel and H. des Abbayes, *Inorg. Chim. Acta*, 1996, **244**, 105.

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