The Way the Three Basic Bricks of the B.A.S.I.C. (BINO–ANSA–SPIRO in Cyclophosphazenes) Game are Built: a 121.5 MHz ^{31}P NMR Kinetic Study

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Abstract

The 121.5 MHz ^{31}P NMR was used for elucidating kinetically the way the three basic bricks of the B.A.S.I.C. game are built. The formations of these three bricks obey second-order rate laws. The SPIRO loop is formed much faster than BINO bridge or ANSA arch. The 1,3-diaminopropane behaves as a genuine primary mono-amine. Kinetic data can be expressed in terms of very simple geometrical parameters such as 'stability or not' of the *n*-membered cyclic structures.

Introduction

The reactions of $N_3P_3Cl_6$ with poly-amines give unique products the structures of which depend on the nature of the poly-amine. 1,3-diaminopropane (DAP) and 1,4-diaminobutane (putrescine) lead to SPIRO configurations, 1,5-diaminopentane (cadaverine) to BINO structures, spermidine and spermine to SPIRO–BINO and DISPIRO–BINO entities [1]. Moreover, the bis-(2-aminoethyl)-ether, $H_2N-(CH_2)_2-O-(CH_2)_2-NH_2$, isologous of cadaverine, yields neat ANSA derivatives [2]. In other words, there exists a sort of molecular additivity within the field of polyamine-linked cyclophosphazene chemistry, any molecule containing two or more SPIRO loops, BINO bridges and/or ANSA arches being synthesized on demand. This 'box of bricks' chemical game was labelled as B.A.S.I.C. [3].

Then, owing to the remarkable additive character of this kind of molecular Lego, we were urged to investigate the way the 3 basic bricks, *i.e.* the BINO, ANSA and SPIRO ones, are built. Indeed, if the aminolysis of $N_3P_3Cl_6$ by primary and secondary mono-amines was widely investigated, mainly by Shaw [4], Goldschmidt [5] and Krishnamurthy [6], no kinetics study for aminolysis by di-amines and *a fortiori* by poly-amines was ever carried out, to our knowledge at least.

In our case, we used for this purpose the performances of high-field ^{31}P NMR which proved recently to be a very adequate tool for the assignment of molecular structures and preferred conformations within the cyclophosphazenic series [7–12].

Experimental

^{31}P NMR spectra were recorded on a BRUKER MSL 300 instrument operating at 121.5 MHz for ^{31}P. This spectrometer is equipped with an Aspect 3000 computer and a process controller. The 90° pulse length was *ca.* 4.5 μsec for ^{31}P using the low power RF amplifier. Spectra were collected by co-addition of 16 scans with 45° flip angle pulses and a recycling time of 3 s. These conditions are optimal to take into account the T_1 relaxation times (*ca.* 2–3 s depending upon the sample nature and the temperature). Measurements were performed with 5 mm NMR tubes containing 0.300 ml of a (1:1) mixture of 0.05 M solutions of $N_3P_3Cl_6$ and diamine each. A very large excess of triethylamine (0.075 ml, used for picking up hydrogen chloride from the reaction) was introduced in the medium in order not to have to take Et_3N concentration into account in the mathematical treatment of data.

The mixing of reagents was done at −50 °C. Tubes are then introduced into the pre-cooled probe. For each temperature, 15 FID (16 scans each) were recorded at one minute intervals. $CDCl_3$ was used as the solvent because of the solubility of $Et_3N \cdot HCl$. Broad-band proton decoupling was achieved using a WALTZ 16 type asynchronous procedure. All chemical shifts are given as positive to low-field and refer to external H_3PO_4.

Kinetics of the BINO Brick Formation

The ^{31}P spectrum of the kinetic product, presented in Fig. 1, is identical to the one of the synthetic

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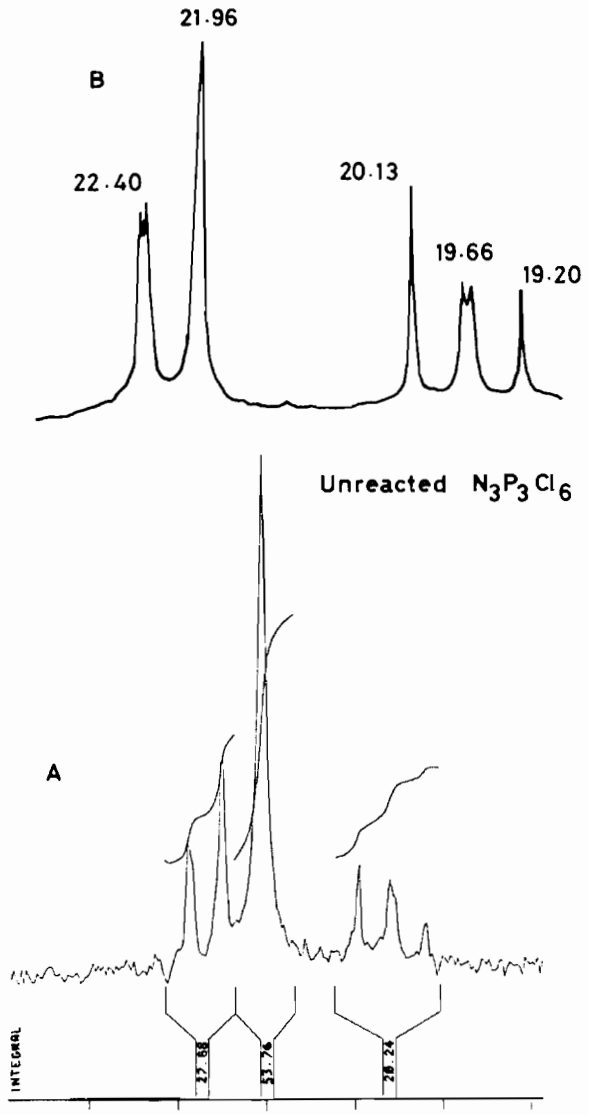

Fig. 1. ^{31}P NMR spectra (A) of the BINO kinetic product (121.5 MHz) and (B) of the BINO synthetic product (101.3 MHz).

BINO derivative [1], *i.e.* a PCl_2 doublet at 21.96 and 22.40 ppm and a *P*ClNH triplet centered on 19.66 ppm, $^2J(PP) = 47.1$ Hz.

NMR data for 1,6-diaminohexane as the reactant are reported in Fig. 2. These data were mathematically treated as usual by suitable softwares. The reaction of the 1,6-diaminohexane on $N_3P_3Cl_6$ obeys a second-order rate law. Such an order is in agreement with a bimolecular SN2(P) type mechanism, analogous to the one described by Katti and Krishnamurthy [6] for the reaction of Me_2NH with $N_3P_3Cl_6$. This mechanism involves a five-coordinate phosphorus intermediate in a rapid pre-equilibrium step, the rate-determining step being the decomposition of this intermediate with the formation of the BINO brick.

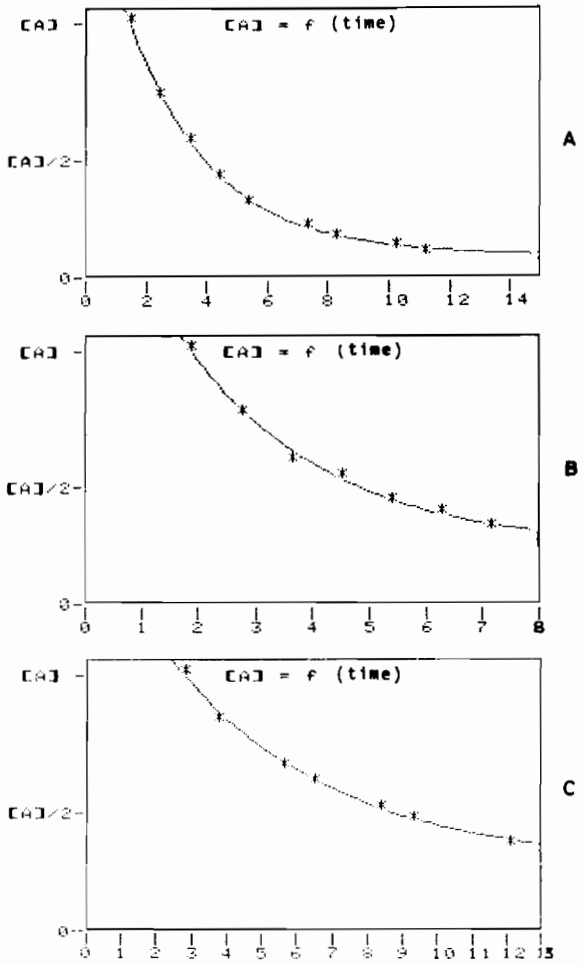

Fig. 2. NMR kinetic data (121.5 MHz) for the BINO product at 295 (A), 285 (B) and 275 (C) K.

Rate constants ($dm^3\ mol^{-1}\ s^{-1}$) for 275, 285 and 295 K are 0.067, 0.173 and 0.188, respectively.

Kinetics of the ANSA Brick Formation

NMR measurements were consistently performed in $CDCl_3$. However, Fig. 3 shows that the final kinetic product we observed in this solvent differs from the genuine ANSA derivative commonly synthesized in acetonitrile [2]. The spectrum of the latter comprises a *P*ClNH doublet at 21.29 and 19.76 ppm and a PCl_2 triplet centered on 27.18 ppm, $^2J(PP) = 58.1$ Hz (BRUKER WM 500, in dimethylacetamide–acetonitrile (1:1), with H_3PO_4 as the standard). In contrast, the spectrum of the kinetic product in $CDCl_3$ reveals a doublet at 21.1 and 20.8 ppm and a triplet centered on 19.0 ppm, $^2J(PP) = 36.4$ Hz. Obviously, the kinetic product is the intermediate DANGLING [13] species in which the diamino reactant is linked through only one of its two primary amino functions. Its spectrum is close indeed to the one of a BINO

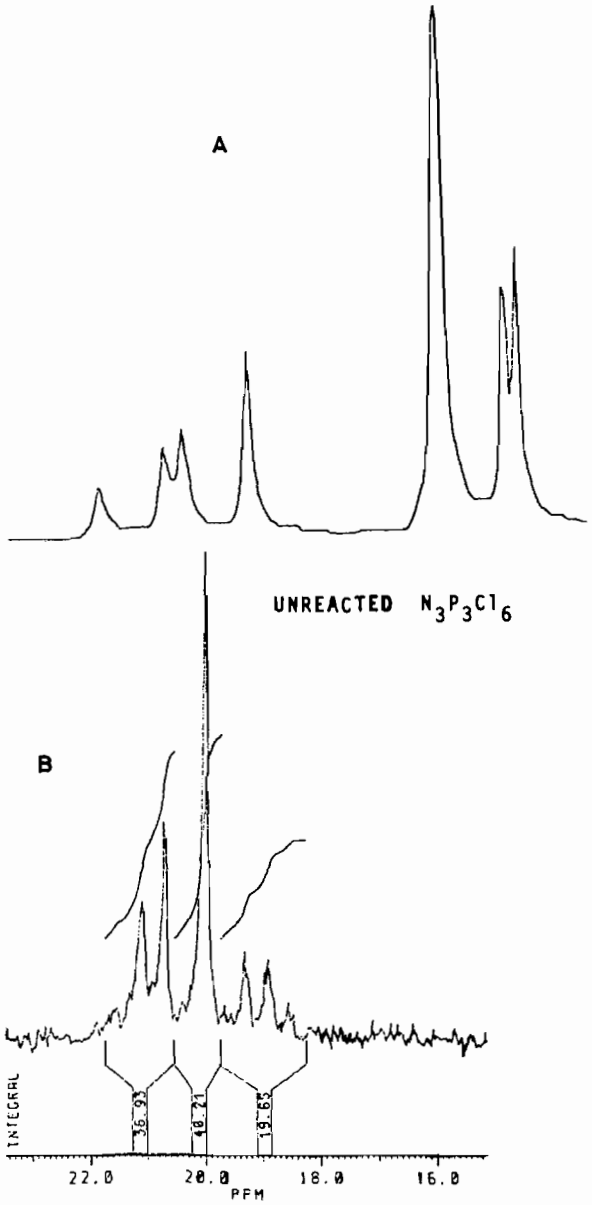

Fig. 3. ^{31}P NMR spectra (A) of the ANSA synthetic product (36.4 MHz) and (B) of the kinetic ANSA intermediate (121.5 MHz).

species (see above), considering chemical shifts at least. In other words, the reaction of bis(2-amino-ethyl)-ether on $N_3P_3Cl_6$ yields a kinetic intermediate which is parent with the thermodynamic intermediate isolated by Harris and Williams [14] on the first step of their synthesis of the $N_3P_3Cl_3(CH_3)[HN–(CH_2)_3–O]$ANSA derivative (Fig. 4).

NMR data are reported in Fig. 5 for measurements at 275, 285 and 295 K. The synthesis of the kinetic intermediate obeys a second-order-rate law as for the BINO derivative. Rate constants ($dm^3\ mol^{-1}\ s^{-1}$) are 0.052, 0.056 and 0.241, respectively.

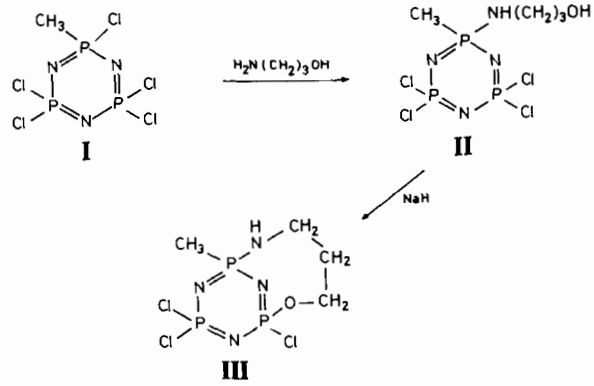

Fig. 4. Reaction pathway for the synthesis of the ANSA derivative from Harris and Williams [14].

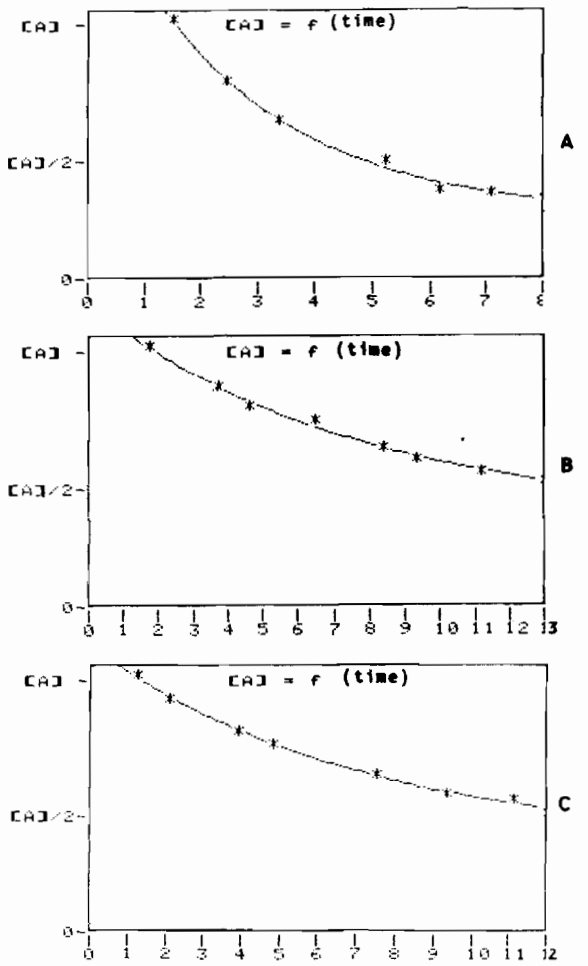

Fig. 5. NMR kinetic data (121.5 MHz) for the kinetic ANSA intermediate at 295 (A), 285 (B) and 275 (C) K.

A comparison of these rate constants to the ones we found for the BINO derivative shows that the formation of the ANSA intermediate (and, probably, of the ANSA itself) runs about as fast as that of the BINO species. This is consistent with the times of

TABLE I. Rate Constants and Activation Parameters for the Formation of BINO, ANSA and SPIRO Basic Bricks

Compound	k ($dm^3\ mol^{-1}\ s^{-1}$) (T (K))	$\Delta H^{\ddagger}$ (KJ mol^{-1})	$\Delta S^{\ddagger}$ (J $mol^{-1}\ K^{-1}$)
BINO	0.188 (295) 0.173 (285) 0.067 (275)	38.0	−128.2
ANSA (intermediate)	0.241 (295) 0.056 (285) 0.052 (275)	56.2	−68.9
SPIRO	0.071 (265) 0.033 (255) 0.024 (245)	26.8	−165.7
$MeNH_2$ [5]		23.0	−169.0
Me_2NH [6]		20.7	−128.0

reaction which are necessary to get the ANSA and BINO compounds in the lab: both preparations require indeed 2 days when working in acetontrile at ambient temperature.

Kinetics of the SPIRO Brick Formation

NMR measurements were consistently performed once more in $CDCl_3$. In a first step, we investigated the 275–295 K range but the order rates we found were definitely meaningless, owing to the extremely large reaction rates at such temperatures with respect to the two previous cases.

Thus, NMR data were recorded at lower temperatures than above, *i.e.* at 245, 255 and 265 K. Then, correct order rates and rate constants could be obtained: the reaction of the 1,3-diaminopropane on $N_3P_3Cl_6$ obeys a second-order rate law with rate constants ($dm^3\ mol^{-1}\ s^{-1}$) equal to 0.024, 0.033 and 0.071 for 245, 255 and 265 K, respectively.

Results and Discussion

The kinetic data, namely rate constants k, enthalpies of activation $\Delta H^{\ddagger}$ and entropies of activation $\Delta S^{\ddagger}$ for the three reactions studied here are gathered in Table I together with $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ obtained for $MeNH_2$ [5] and Me_2NH [6], respectively.

First of all, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values for the SPIRO brick are very close to the ones obtained by Goldschmidt and Licht [5] for the primary amine $MeNH_2$. In other words, the reaction of 1,3-diaminopropane on $N_3P_3Cl_6$ is governed by the rate of the graft of the first primary amino group, the second graft occurring more rapidly yet in sequence. Thus, the 1,3-diaminopropane behaves as a genuine primary mono-amine.

The formation of the BINO brick is less facile than the one of the SPIRO brick, as far as $\Delta H^{\ddagger}$ values are concerned. The $\Delta S^{\ddagger}$ (BINO) value, conversely smaller than $\Delta S^{\ddagger}$ (SPIRO), is quite close to the $\Delta S^{\ddagger}$ (Me_2NH) value.

Finally, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values for the ANSA brick are the largest and the smallest, respectively, in the series, making the influence of the oxygen atom of the diamino chain conspicuous.

An overall survey of Table I calls for the following remarks:

1 – The formations of the three basic bricks of the B.A.S.I.C. game obey second-order rate laws;

2 – The SPIRO brick is formed much faster than BINO and ANSA bricks;

3 – The 1,3-diaminopropane behaves as a genuine primary mono-amine;

4 – The 1,6-diaminohexane is less reactive than the 1,3-diaminopropane, its $\Delta S^{\ddagger}$ value being the same as the one of the secondary mono-amine Me_2NH;

5 – The bis-(aminoethyl)-ether is less reactive than the two other di-amines, in $CDCl_3$ and within the 245–295 K range at least.

These concluding remarks can be expressed in terms of simple geometrical reasons: (i) the graft of the 1,3-diaminopropane on $N_3P_3Cl_6$ in the SPIRO configuration is definitely favoured by the very high stability of a six-membered loop which makes the two primary amino functions prone to attack one P atom rather simultaneously; (ii) a lengthening of the di-amine cancels its capability to give stable n-membered loops and the two primary amino functions are then inclined to link two N_3P_3 moieties in a BINO configuration rather than to loop on the same P atom or on two different P atoms of a N_3P_3 entity; (iii) in contrast, the bis-(aminoethyl)-ether, which is too long to give a SPIRO loop (eight-membered loop), is small enough to make an ANSA arch on the same N_3P_3 moiety. Incidentally, the oxygen atom of the bis-(aminoethyl)-ether plays a determinant role in the formation of the ANSA arch, the isologous cadaverine yielding a neat BINO structure.

Conclusions

The 121.5 MHz ^{31}P NMR was used for elucidating kinetically the way the three basic bricks of the B.A.S.I.C. game are built. The formation of the SPIRO loop runs much faster than the ones of the BINO bridge and of the ANSA arch. All the kinetic data (rate constants, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values) reflect actually the 'capability or not' for the difunctional reagents to link the cyclophosphazenic species in a 'stable or not' *n*-membered cyclic configuration. Similar kinetics studies on the way the SPIRO–BINO and DISPIRO–BINO configurations are obtained upon reaction of polyfunctional reagents on $N_3P_3Cl_6$ are under investigation.

References

1 J.-F. Labarre, *Top. Curr. Chem., 129*, 173 (1985).
2 P. Castera, J.-P. Faucher, J.-F. Labarre and B. Perly, *J. Mol. Struct., 160*, 365 (1987).
3 F. Sournies, J.-F. Labarre, P. J. Harris and K. B. Williams, *Inorg. Chim. Acta, 90*, L61 (1984), and ref. 14 therein.
4 S. K. Das, R. Keat, R. A. Shaw and B. C. Smith, *J. Chem. Soc., Dalton Trans.*, 5032 (1965).
5 J. M. E. Goldsmidt and E. Licht, *J. Chem. Soc., Dalton Trans.*, 107 (1981).
6 K. V. Katti and S. S. Krishnamurthy, *J. Chem. Soc., Dalton Trans.*, 285 (1985).
7 G. Folcher, B. Perly, G. Guerch, J.-F. Labarre, F. Sournies and L. Vidaud, *J. Mol. Struct., 159*, 113 (1987).
8 B. Perly, L. Vidaud, J.-P. Bonnet and J.-F. Labarre, *J. Mol. Struct., 161*, 175 (1987).
9 B. Perly, P. Berthault, L. Vidaud, G. Guerch, J.-F. Labarre and F. Sournies, *J. Mol. Struct., 162*, 87 (1987).
10 P. Berthault, B. Perly, L. Vidaud and J.-F. Labarre, *J. Mol. Struct., 162*, 97 (1987).
11 B. Perly, P. Berthault, L. Vidaud and J.-F. Labarre, *J. Mol. Struct.*, 1988, in press.
12 B. Perly, P. Berthault, J.-P. Bonnet and J.-F. Labarre, *J. Mol. Struct.*, 1988, in press.
13 H. A. Al-Madfa, M. B. Hursthouse, H. G. Parkes, L. S. Shaw and R. A. Shaw, *Phosphorus Sulfur, 28*, 203 (1986).
14 P. J. Harris and K. B. Williams, *Inorg. Chem., 23*, 1495 (1984).