# A Theoretical Conformational Analysis of Spiro Loops in Spirocyclotriphosphazenes

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During the past two decades there has been controversy in the literature concerning the so-called SPIRO [1] *versus* ANSA [2] dilemma related to the molecular structure of products of the reaction of hexachlorocyclotriphosphazene, $N_3P_3Cl_6$, with difunctional reagents.

Conclusive evidence – from X-ray investigations – for a SPIRO structure were recently obtained in several cases: (i) upon reaction of $N_3P_3Cl_6$ with 1,3-diaminopropane both with (1:1) (compound **I**) [3–5], (1:2) and (1:3) (compound **II**) [6, 7] stoichiometric conditions (ii) upon reaction of $N_3P_3Cl_6$ with 1,4-diaminobutane [4, 8] in (1:1) conditions (compound **III**) (iii) upon reaction of $N_3P_3Cl_6$ with spermidine, *i.e.*, N-(3-aminopropyl)-1,4-diaminobutane [4, 5] (compound **IV**) and spermine, *i.e.*, N,N′-bis(3-aminopropyl)-1,4-diaminobutane [4, 9] (compound **V**) (iv) upon reaction of $N_3P_3Cl_6$ with ethylene glycol, 1,3-propylene glycol and 1,4-butylene glycol in (1:1) conditions (compounds **VI** to **VIII**) [10] (v) upon reaction of $N_3P_3Cl_6$ with 1,3-propylene glycol in (1:2) conditions (major product compound **IX**) [11] and (vi) in aziridino derivative ($N_3P_3Az_4[HN-(CH_2)_3-NH]$ (compound **X**) [12, 13].

On the other hand, conclusive evidence – from X-ray investigations too – for an ANSA structure were recently provided in two cases (i) upon reaction of $N_3P_3Cl_5(CH_3)$ with 3-amino-1-propanol (compound **XI**) [14, 15] and (ii) upon reaction of $N_3P_3Cl_6$ with 1,3-propylene glycol in (1:2) conditions (minor product compound **XII**) [11].

A critical survey of the whole set of SPIRO structures shows that SPIRO loops display essentially two types of conformation, hereinafter coded as *twisted* and *chair* (Table I). The chair conformation is the most common, the twisted one occurring only in **I** and **III** structures.

Incidentally, a third type of conformation, coded as half-chair, is observed for compound **IV** [5]. This is the unique example of quasi planar conformation made up-to-now conspicuous in spirocyclotriphosphazenes.

The linking of cyclophosphazenes to natural polyamines (1,3-diaminopropane, 1,4-diaminobutane, spermidine and spermine) was performed in our laboratory with the aim of increasing the selectivity of antitumoral cyclophosphazenes for tumor cells and decreasing their toxicity for normal tissues. It is known that rapidly proliferating cells have a high capacity for active, carrier-mediated uptake of polyamines [16, 17]. Accordingly, polyamines represent a useful means for targeting chemicals possessing cell-inhibitory capacity to neoplastic tissues.

Such an attempt at the production of more selective antitumor agents looks promising *in vivo* [12, 13]. Moreover, structure–activity relationships seem to emphasize a close dependence of activity on the conformation of the SPIRO loops, as discussed above.

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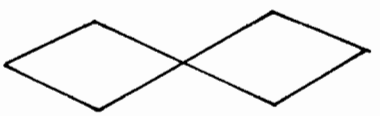
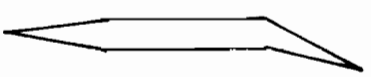
TABLE I. Conformations of Spiro Loops.

| Code | Pattern | Chemicals |
|---|---|---|
| Twisted |  | **I, III** |
| Chair |  | **II, V, VI, VII, VIII, IX, X, XII** |
| Half-chair |  | **IV** |

0020-1693/84/$3.00

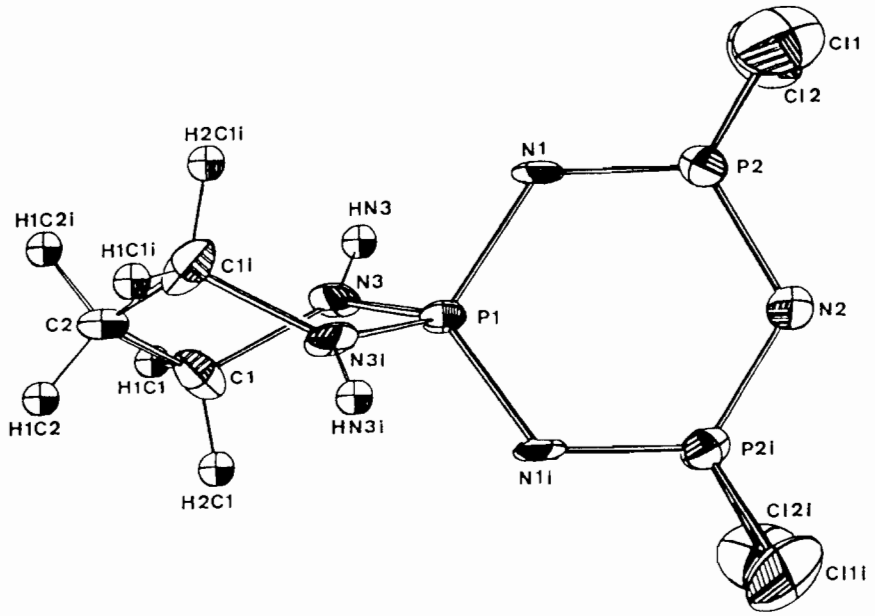



Fig. 1. A perspective view of the twisted loop in $N_3P_3Cl_4[HN-(CH_2)_3-NH]$.

It was thus of interest to investigate which electronic and/or geometrical factors the existence of the three observed SPIRO conformations depends on, in order to design more selective antitumorals from X-ray structures.

As mentioned above only two chemicals, namely **I** and **III**, display twisted SPIRO loops amongst the series. The main feature of their structures when compared to those of other spirocyclotriphosphazenes concerns the neighbourhood of the loop-bearing $P_1$ atom: in **I** for instance (Fig. 1) the presence of the loop pulls $P_1$ away from $N_2$ along the two-fold axis, the endocyclic $P_1-N_1$ and $P_1-N_{1i}$ bonds being much longer (1.605 Å) than the average value (*ca.* 1.58 Å) normally expected for a trimeric cylophosphazenic ring. Consequently the $N_1P_1N_{1i}$ angle is much smaller (111.5°) than that in other trimeric cyclophosphazenes (*ca.* 119°). About the same feature is observed for **III** [8].

In other words, the $N_3P_3$ ring in **I** and **III** is noticeably distorted from the expected quasi-ternary symmetry which exists in other spirocyclotriphosphazenes. Such a distorted ring will be coded below as *stretched* in contrast with 'symmetrical' $N_3P_3$ ring which will be coded as *regular*.

Actually, the packing of **I** and **III** molecules in the unit cell shows remarkable peculiarities: some intermolecular hydrogen bonds, established between nitrogen atoms of one cyclophosphazenic ring and nitrogen atoms of the loop of the neighbour molecule, are clearly evidenced (Fig. 2). Two hydrogen bonds per molecule (2.08 Å), participating with the Van der Waals forces to the cohesion of the crystal, generate a concerted twist of the loop from its free conformation: one hydrogen bond pulls up one N atom of the loop when the second pulls down the other.

Thus, the existence of a twisted conformation – related to a stretched $N_3P_3$ ring – could be due to intermolecular hydrogen bonds which appear only in unit cells of **I** and **III** amongst the series. Then, both the real loop conformation and $N_3P_3$ ring symmetry of free molecules of **I** and **III** would have to be actually closer to the 'normal' ones, *i.e.* to a *chair* conformation for the loop and to a *regular* $N_3P_3$ ring.

Therefore, CNDO/2 formalism [18] was used for computing total energy of the following merged systems for **I**:

1) twisted loop (**T**) *plus* stretched ring (**S**) coded as **TS**;

2) twisted loop (**T**) *plus* regular ring (**R**) coded as **TR**;

3) chair loop (**C**) *plus* stretched ring (**S**) coded as **CS**;

4) chair loop (**C**) *plus* regular ring (**R**) coded as **CR**.

The data were obtained on an Apple 256 K computer by using one of the modules included in an enhanced release of the TRIX software [19]. Two series of coordinates were generated: one from the (**I**) structure (four sets as explained above), the other from the (**X**) structure (four sets also). These sets were coded with the prefix Cl or Az respectively and the suffix **TS** or **TR** or **CS** or **CR** as defined above.

These eight systems were stored on the Profile 5 Mo hard disk of the Apple. Then, emulating a terminal on this microcomputer, we ran the CNDO

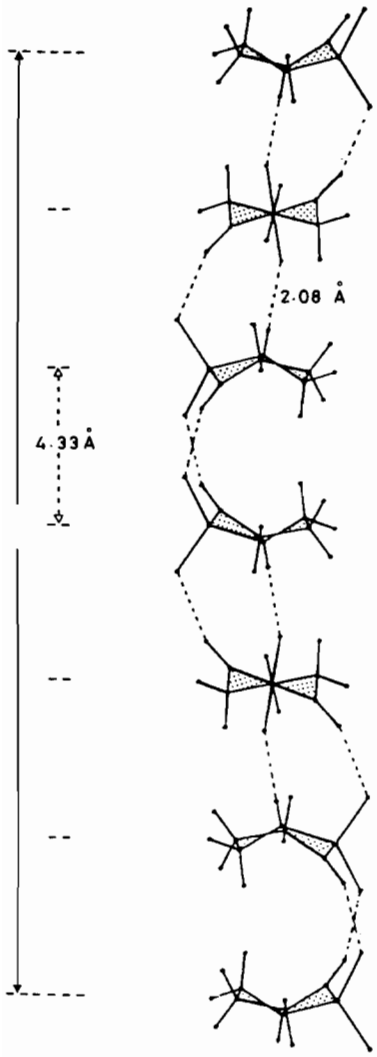



Fig. 2. Pattern of hydrogen bonds in the unit cell of $N_3P_3Cl_4[HN-(CH_2)_3-NH]$.

program in the Computing Center of Toulouse University.

## Results and Discussion

The total energy values for the eight merged systems are gathered in Table II. Whatever the Cl or Az set considered, the **CR** combination appears to be definitely preferred. In other words, the **TS** pattern observed crystallographically for **(I)** may as predicted be related to intermolecular hydrogen bonds in the unit cell (see above).

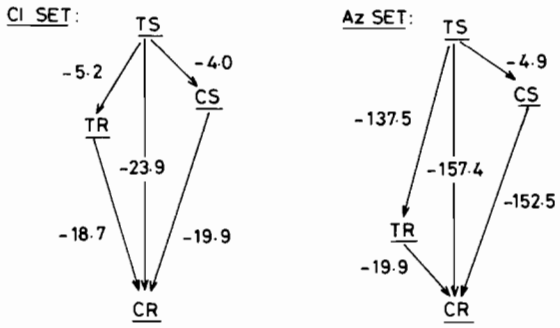
Table III visualizes the two possible pathways, both for the Cl and for the Az series, going from the **TS** to the **CR** spatial arrangement. This table shows that:

1) the **T** → **C** distortion is energetically very facile, so much that $N_3P_3$ ring is of S type: gaps of energy

TABLE II. Total Energies (kcal $mol^{-1}$)

| Suffix / Prefix | TS | TR | CS | CR |
|---|---|---|---|---|
| Cl | −108320.2 | −108325.4 | −108324.4 | −108344.1 |
| Az | −139813.2 | −139950.7 | −139818.1 | −139970.6 |

TABLE III. The Possible Pathways for the **TS** → **CR** Transition (energy values in kcal $mol^{-1}$).




are indeed about 4 to 5 and 19 to 20 for **TS** → **CS** and **TR** → **CR** in the Cl and Az diagrams respectively;

2) Similarly, the **S** → **R** modification is easier by 15 kcal $mol^{-1}$ when the $N_3P_3$ ring is twisted **(T)** than when it is regular **(R)**;

3) the **TS** → **TR** and **CS** → **CR** transitions are forbidden when ligands are aziridinyl groups whereas they may be envisaged for Cl homologues. This means that Az ligands force the $N_3P_3$ ring to be regular, even when intermolecular forces are present in the unit cell. Such a tendency has been previously observed for other aziridinocyclotriphosphazene derivatives [20–23];

4) For the Cl part of Table III, the **CR** → **TS** jump would need 24 kcal $mol^{-1}$, *i.e.* 12 kcal $mol^{-1}$ per hydrogen bond. This value looks large when compared to data from literature [24] but CNDO/2 calculations are intrinsically overestimating bicentric terms of the energy matrix [25].

We computed by the same technique the total energy of the $N_3P_3Cl_6\cdots NH_3$ hypersystem (Fig. 3) in order to approach the energy of a 2.08 Å hydrogen bond analogous to the ones which exist in the unit cell of **(I)**. Bicentric E(N···H) energy term is found to be equal to 11.5 kcal $mol^{-1}$, *i.e.* about 12

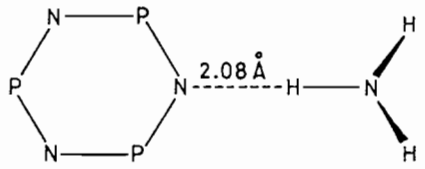



Fig. 3. The $N_3P_3Cl_6\cdots NH_3$ hypersystem.

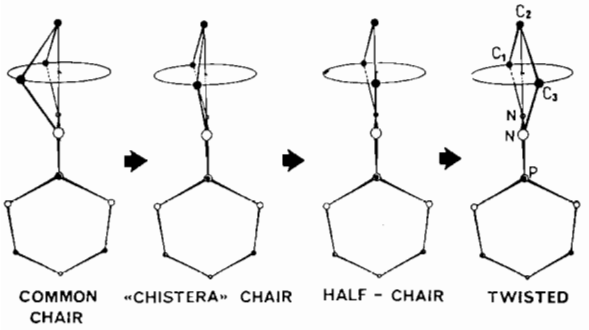



Fig. 4. A visualization of the chair to twisted loop transition in spirocyclotriphosphazenes.

kcal $mol^{-1}$, in this way. This value is consistent with the estimation made above from Table III about the energy of intermolecular hydrogen bonds in the unit cell of **I**.

Incidentally, 24 kcal $mol^{-1}$ are enough for the **CR** → **TS** transition in the Cl system in contrast with the Az one, where only **CR** → **TR** could be envisageable.

## Conclusion

A theoretical conformational analysis (within the CNDO/2 approximation) of regular (**R**) *versus* stretched (**S**) and of chair (**C**) *versus* twisted (**T**) characters of $N_3P_3$ ring and SPIRO loop respectively was performed. The **CR** pattern appears to be preferred in any case, except when strong intermolecular hydrogen bonds exist in the unit cell. Such hydrogen bonds make the **TS** form observable in $N_3P_3Cl_4[HN-(CH_2)_3-NH]$ SPIRO derivative and could favour the **TR** form (but not the **TS** form) in its peraziridino homologue.

As a conclusion, the remarkable antitumoral activity *in vivo* of aziridinospirocyclotriphosphazenes may be related to a *chair* SPIRO loop* grafted on a *regular* cyclotriphosphazenic ring.

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*A deep survey of X-ray structures now available for spirocyclotriphosphazenes shows the following: the P–$C_2$ distance (Fig. 4) stays constant (3.10 ± 0.04 Å) as well as the P–$C_1$ and P–$C_3$ distances which are generally both equal to 2.68 ± 0.04 Å. $C_1$–P–$C_3$ and $C_1$–$C_2$–$C_3$ angles remaining constant and equal to 124.6 ± 1 and 112.3 ± 1°, respectively, it appears that all the conformations which exist in spirocyclotriphosphazenes depends actually on a simple rotation of $C_3$ atom on the base of a cone (apex in P: 124.6°, symmetry axis: P–$C_2$).

Thus, $C_2$ atom belonging to the corresponding N P N exocyclic plane, common-chair, 'chistera' chair, half-planar and twisted conformations proceed from various relative locations of $C_1$ and $C_3$ atoms on the base of the cone.