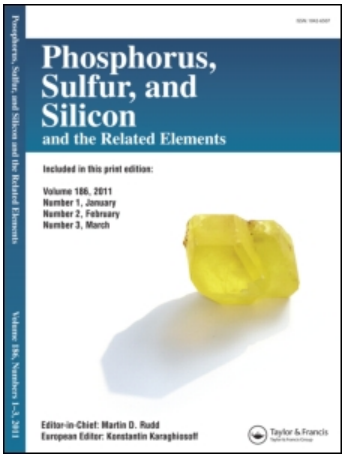

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NMR SPECTRA AND STEREOCHEMISTRY OF DIASTEREOISOMERIC 4,5-DIPHENYL-CYCLOPHOSPHAMIDES

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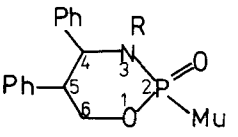
The conformational distribution and relative configuration of four diastereoisomeric pairs of 4,5-diphenyl-cyclophosphamides and their *N*-methyl analogues were determined by means of ^{1}H, ^{13}C, ^{31}P NMR and IR spectroscopy.

The solution stereochemistry of cyclophosphamide derivatives is of basic interest not only in connection to the conformational properties of the 1,3,2-oxazaphosphorinane ring but also due to the potential anticancer activity of such compounds. Thus, several comprehensive studies were directed towards the conformational elucidation of cyclophosphamide and some of its alkyl derivatives by means of NMR spectroscopy and other physical methods.[1–6]

Recently, four diastereoisomeric 4,5-diphenyl-cyclophosphamides (**1–4**) and their *N*-methyl analogues (**5–8**) have been synthesized by some of us.[7] (Scheme 1). The aim of the present study is to determine the relative configurations and the favoured conformations of these compounds in solution by means of ^{1}H, ^{13}C, ^{31}P NMR and IR spectroscopy.



1 – 4 , R = H
5 – 8 , R = CH_3
Mu = $N(\underset{\alpha}{CH_2}\underset{\beta}{CH_2}Cl)_2$

SCHEME 1

RESULTS AND DISCUSSION

The first-order ^{1}H NMR parameters and the ^{31}P chemical shifts of compounds **1–8** are presented on Table I, the ^{13}C NMR data are given on Table II and the IR data on Table III.

The relative configuration with respect to the C-4,5 bond for all compounds was assumed on the basis of the known configuration of the synthetic precursors (trans- and cis-3-amino-2,3-diphenyl-propanols for compounds **1**, **2**, **5**, **6** and **3**, **4**, **7**, **8**, resp.);[7] it was also confirmed by the present NMR data. The main stereochemical problems were to establish the relative configuration at phosphorus as well as the favoured conformations of all compounds.

TABLE I

^1H and ^{31}P NMR parameters for diastereomeric 4,5-diphenyl cyclophosphamides **1–8** (in $CDCl_3$)

Comp.	Proton chemical shifts (δ, ppm) and coupling constants J (Hz)																δ ^{31}P ppm
	H-4	H-5	H-6$_A$	H-6$_B$	NH[a] (NCH$_3$)	N(CH$_2$CH$_2$Cl)$_2$	Ph	J_{45}	J_{4P}	J_{4NH}	J_{56_A}	J_{56_B}	J_{NHP}	$J_{6_A6_B}$	J_{6_AP}	J_{6_BP}	J_{CH_3P}	
1	4.61 td	3.4 m	4.38 ddd	4.50 ddd	3.08 bd	3.35–3.75 m	6.98–7.25 m	9.5	9.5	2.5	4.1	10	7.0	−11.0	17.2	5.3	—	9.8
2	4.78 d	3.13 td	4.26 ddd	4.76 td	2.77 bs	3.55–3.75 m	6.93–7.22 m	11	b	b	4.2	11.5		−11.0	23.5	2.4	—	13.5
3	4.79 m	3.55 m	4.76 m	4.26 ddd	3.00 t	3.49–3.74 m	6.65–7.20 m	5	17	4.0	7.2	3.3	4.5	−11.3	5	18.8	—	10.0
4	5.20 t	3.31 q	4.66 ddd	4.94 ddd	2.72 bs	3.48–3.80 m	6.83–7.21 m	3	3.5	b	3.6	3.5		−11.5	19.5	4.6	—	15.0
5	4.58 dd	3.28 m	4.48 m	4.40 m	2.54 d	3.35–3.70 m	7.15–7.46 m	6.7	18.0	—	3	6.5	—	−11	9	14	9.9	12.8
6	4.34 d	3.23 td	4.18 ddd	4.75 td	2.34 d	3.55–3.76 m	6.88–7.20 m	10.8	b	—	4.1	11.6	—	−11.4	23.2	3.4	10.7	16.5
7	4.46 dd	3.5 m	4.82 td	4.11 ddd	2.53 d	3.43–3.77 m	6.55–7.17 m	5.4	18.9	—	11.5	3.2	—	−11.0	2.0	22.8	9.6	11.7
8	4.34 m	4.22 m	4.67 q	4.45 m	2.56 d	3.42–3.78 m	6.60–7.23 m	4.5	3	—	11.4	3.6	—	−11	11	8.0	11.0	13.6

[a] Proved via D_2O-exchange;
[b] Splitting not observed ($J < 1.0$ Hz)

TABLE II

^{13}C NMR chemical shifts (δ, ppm) and $^{13}C-^{31}P$ coupling constants (Hz, in parentheses) for diastereoisomeric 4,5-diphenyl-cyclophosphamides **1–8** (in $CDCl_3$)

Comp.	C-4	C-5	C-6	C-α	C-β	C_{ipso}^{Ph-4}	C_{ipso}^{Ph-5}	$C_{o,m}^{Ph}$	C_{p}^{Ph}	CH_3N
1	63.2	50.0 (8.2)	71.2 (7.3)	42.3	48.7 (3.4)	141.4 (6)	136.8	127.1; 128.1; 128.6; 128.7	127.7; 128.1;	—
2	62.7	50.0	70.1 (5.6)	42.4	49.0 (3.7)	141.1 (12.0)	136.0	127.0; 128.3; 128.5; 128.7	127.7; 128.2	—
3	62.4	46.2	66.4	42.4	49.1	139.1	136.6	128.0; 128.1; 128.2; 128.7	127.5; 127.7	—
4	60.2 d	45.7 d	70.5 t	42.3 t	48.6 t	140.0 (10)	137.2	127.0; 127.8; 128.2; 129.2	127.0; 127.9	—
5	70.6	49.6	68.1 (6.1)	42.4	49.9 (3.5)	140.3	138.2	127.7; 127.8;	128.8; 128.9	33.5
6	70.7 d	51.2 d	68.7 t	42.3 t	49.9 t	139.3 (10)	136.4	127.5; 128.3; 128.5; 128.6	127.9; 128.5	33.2
7	70.7	47.0 (3.7)	64.8 (7.0)	42.5	50.0 (3.7)	136.4	135.8	128.0; 128.2; 128.3; 128.9	127.5; 127.7	34.2 (2.9)
8	69.3	45.9 (13.4)	67.5 (6.1)	42.4	50.1 (3.5)	137.4 (5.6)	136.2	128.2; 128.5	127.5; 128.0	34.5

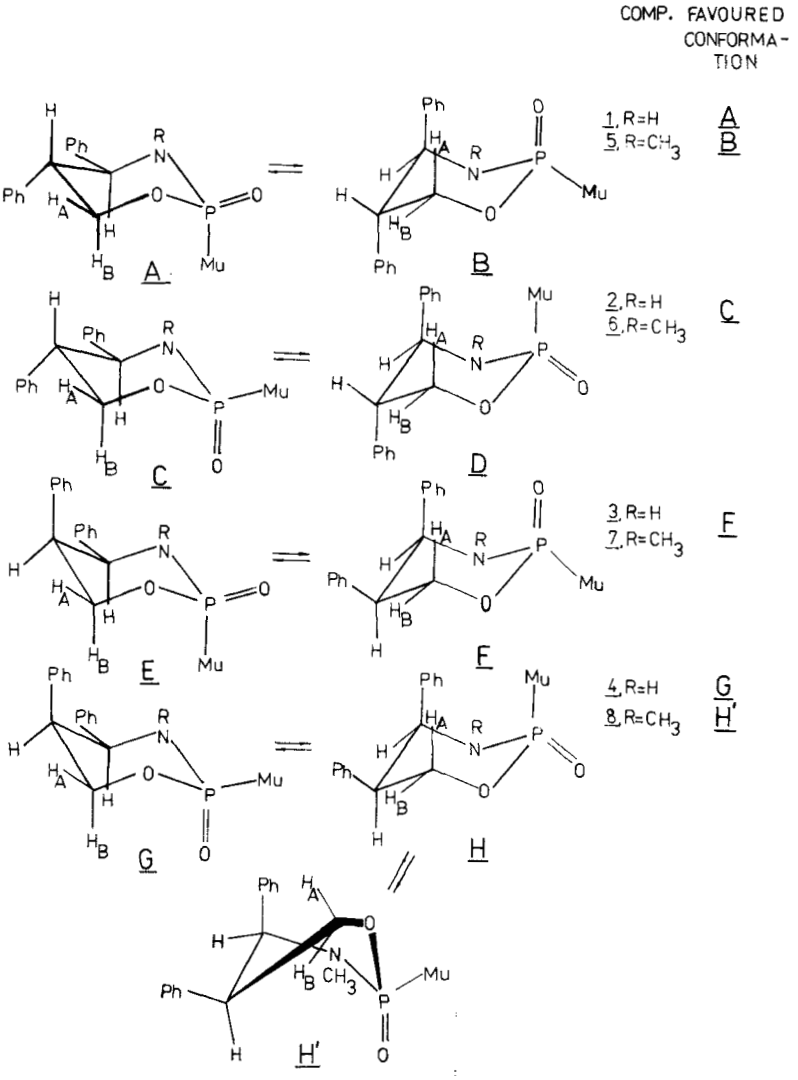
The compounds **1–8** are presented as chair conformers on Scheme 2. The following stereochemical conclusions were reached mainly on the basis of the ^1H NMR data and are supported also by the ^{31}P and ^{13}C NMR data.

It has been found that in cyclophosphamide[2] and its 5,5-dimethyl derivative[6] the $N(CH_2CH_2Cl)_2$ group is predominantly equatorial in $CDCl_3$ solution. Inspection of the ^1H NMR data for the 4,5-trans-isomers **1**, **2**, **5**, **6** reveals that compounds **2**, **6** exist as practically pure chair conformers with H-5 in axial position. This conclusion is supported by the high J_{45}- and J_{56B}-values as well as by the J_{6AP} values which are on the upper limit observed so far for cyclophosphamides.[6] All this evidence strong indicates that the stereochemistry of **2**, **6** is represented by the chair form *C*, with all three large substituents in equatorial position. Comparison of the ^1H NMR data for **1** and **5** shows that their conformational preference differs. From the values of J_{6AP} and J_{6BP} and assuming $J(6eq, P) = 24$ Hz and $J(6ax, P) = 2$ Hz it can be estimated in the usual manner[5,6]

TABLE III

IR frequencies of compounds **1–8**, cm^{-1}, $3 \cdot 10^{-3}$ M in CCl_4

Comp.	PO	free	ν_{NH}	H bonded
1	1236	3359, 3390, 3421		3170
2	1238	3396, 3421		3195
3	1237	3380, 3420		3201
4	1240	3349, 3397		3172
5	1234	—		—
6	1230	—		—
7	1219	—		—
8	1244	—		—



SCHEME 2

that the population ratio of forms *A* and *B* is 70:30 and 35:65 for compounds **1** and **5**, resp. This significant conformational effect amounts to ca. 1.0 kcal/mol change in equilibrium upon *N*-methyl substitution. Similar effect has been observed for *N*-phenyl substituted cyclophosphamides and attributed to steric interaction between the *N*-phenyl group and the axial *N*-alkyl substituent at the P-atom.[6] In our case it is more likely that the effect is primarily due to interaction of N-methyl group with the equatorial 4-phenyl group as a result of some ring flattening caused by a partial double N(3)-P bond character. In other words, the effect may be similar to the familiar allylic strain.[10,11]

These stereochemical conclusions are supported also by the ^{31}P chemical shift data. As a rule, the δ-values are larger for compounds with equatorially oriented

substituent at phosphorus[2,6] which is observed also in our case. For diastereoisomer **4** with cis-oriented 4,5-diphenyl substituents, the small J_{45}-value as well as the absence of a large vicinal H-5/H-6 coupling excludes a favoured axial orientation of H-5 in a chair conformer. On the basis of the higher δ_P-value as well as the deshielding of H-4 and H-6B (typical for protons in syn-axial orientation to a P=O bond[2,5]) we assumed that the stereochemistry of compound **4** is represented by *G* (estimated population on the basis of the J_{6AP}- and J_{6BP}-values ca. 85%).

The ^1H and ^{31}P NMR data for **3** are in agreement with a favoured chair form *F*, populated about 80%.

N-Methylation leads to conformational changes also in the case of the cis-4,5-diphenyl substituted isomers. In analogy to the results for compounds **1** and **5**, the *N*-methylation of **3** leads to a practically pure conformation *F* for compound **7**. For **8**, the ^1H NMR data are in agreement with a dominating twisted form (*H'*), presumably favoured by the avoidance of both the N-ME/4-Ph and the 2,4-syn-axial P-Mu/4-Ph interactions expected for *G* and *H*, resp. Twisted conformers have been already assumed for other cyclophosphamide derivatives and it has been claimed that they are of very similar energy as compared to the chair forms.[4–6]

An additional evidence for the twisted form *H'* is the lower value of 19 Hz for the sum ($J_{6AP} + J_{6BP}$) as compared to its relative constancy (23–25 Hz) found for all other compounds and observed also for other cyclophosphamides where only chair conformers were assumed.[6]

It should also be noted that in all compounds the signal of H-6(axial) is at lower field that of H-6(equatorial).

The ^{13}C NMR chemical shifts (Table II) correspond to those observed for cyclophosphamide,[7] taking into account the expected substituent effect of the phenyl groups at C-4,5. An important criterion permitting the determination of equatorial 4-phenyl orientation in such compounds may be the observance of a large vicinal coupling C_{ipso}/P due to their antiperiplanar orientation.

The IR data (Table III) for compounds **1–8** are in agreement with their structure and also with data published for analogous compounds,[2,6] but are of little (if any) value for the stereochemical assignment.

In conclusion, it may be stated that the conformational distribution for the cis- and trans-4,5-diphenyl-cyclophosphamides **1–8** studied in this work is strongly affected, among other factors, also by the N-3 substitution. The latter could lead to a preference of a chair form with diaxial phenyl groups (*B*), unlike other cases of cyclophosphamide derivatives[4] where the phenyl groups tend to avoid axial orientation.

EXPERIMENTAL

The ^1H, ^{31}P and ^{31}C NMR spectra were measured on a Bruker WM-250 spectrometer at 250.1, 101.2 and 62.9 MHz, respectively at ambient temperature, using solutions in $CDCl_3$. The proton and ^{13}C chemical shifts are with respect to internal TMS, whereas ^{31}P chemical shifts are downfield from external 85% H_3PO_4. The analysis of the proton spectra (in some cases strongly overlapped signals) was assisted by decoupling experiments and D_2O exchange. The assignment of the ^{13}C signals was supported by single-frequency off-resonance decoupling.

The IR spectra were measured on a Bruker IFS 113v spectrometer using 10^{-3} *molar solutions in* CCl_4.

REFERENCES

1. B. E. Maryanoff, R. O. Hutchins and C. A. Maryanoff, *Top. Stereochem.* **11,** 187 (1979).
2. D. W. White, D. E. Gibbs and J. D. Verkade, *J. Am. Chem. Soc.* **101,** 1937 (1979).
3. V. L. Boyd, G. Zon, V. L. Himes, J. K. Stalick, A. D. Mighell and H. V. Secor, *J. Med. Chem.* **23,** 372 (1980).
4. W. G. Bentrude, R. O. Day, J. M. Holmes, G. S. Quin, W. N. Setzer, A. E. Sopchik and R. R. Holmes, *J. Am. Chem. Soc.* **106,** 106 (1984).
5. R. R. Holmes, R. O. Day, W. N. Setzer, A. E. Sopchik and W. G. Bentrude, *J. Am. Chem. Soc.* **106,** 2353 (1984).
6. W. N. Setzer, A. E. Sopchik and W. G. Bentrude, *J. Am. Chem. Soc.* **107,** 2083 (1985).
7. M. Ivanova and M. J. Lyapova, to be published.
8. W. G. Bentrude and J. H. Hargis, *Chem. Commun.* 1113 (1969).
9. W. Egan and G. Zon, *Tetrahedron Lett.* 813 (1976).
10. F. Johnson, *Chem. Rev.* **68,** 375 (1968).
11. B. G. Kurtev, M. J. Lyapova, S. M. Mishev, O. G. Nakova, A. S. Orahovatz and I. G. Pojarlieff, *Org. Magn. Res.* **21,** 334 (1983).