The preferred conformation of cyclophosphamide

By means of the CNDO technique (Complete Neglect of Differential Overlap) (Pople & Beveridge, 1970) we have examined the conformation of cyclophosphamide (Arnold & Bourseaux, 1958). The starting point is the recent X-ray structural analysis of Garcia-Blanco & Perales, 1972) and the relevant configuration is given in Fig. 1. Table 1 summarizes the angle input to a standard coordinate generating computer program (Quantum Chemistry Program Exchange No. 136, U. Indiana, Bloomington, Ind). In all calculations the ring structure is fixed. The carbon–hydrogen bond length used is 1·08Å, the nitrogen–hydrogen bond, 1·04Å. The basic variable is rotation of the mustard group about the P–N bond—defined by the 3–8–15–16 dihedral angle (Fig. 1a) where the integers used represent the numbering system.

Calculations were made in four sets. In set I (Fig. 1b is a view down the N–P bond) Cl_1 points more or less back toward the ring and the 3–8–9–12 dihedral angle is
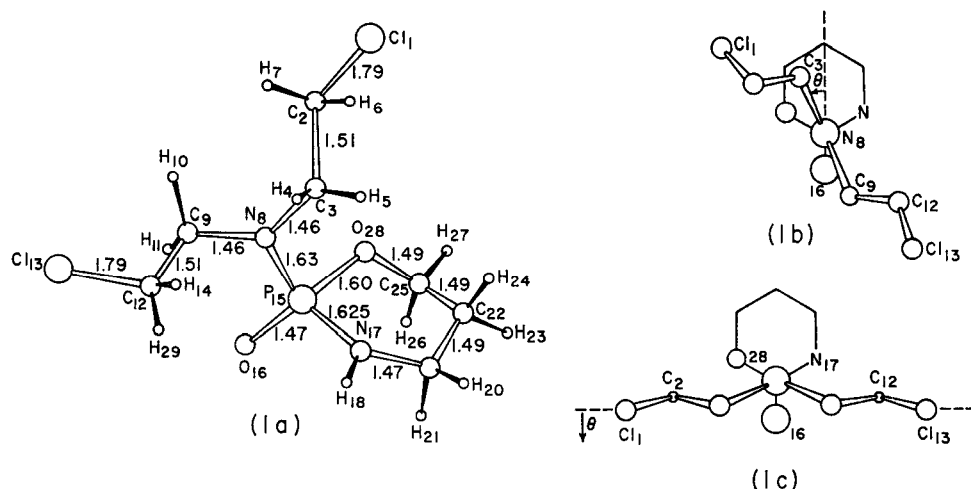

FIG. 1. (*a*) Set I, 0° configuration. Distances in angstroms. (*b*) View down N–P bond for set I. (*c*) View down N–P bond for set IV.

Table 1. *Angle definitions*.*

B–C–D	θ_{BCD}	A–, θ_{ABCD}	B–C–D	θ_{BCD}	A–, θ_{ABCD}
1–2–3	109·47				
2–3–4		1–, 180·0	8–15–16	110·0	3–, 180·0
2–3–5		1–, 60·0	8–15–17	106·8	3–, 106·8
3–2–6		4–, 60·0	15–17–18	119·	8–, 45·0
3–2–7		4–, −60·0	8–15–28	104·7	3–, −60·0
2–3–8		1–, −60·0	15–17–19	118·0	8–, −150·0
3–8–9	120·0	2–, −60·0	17–19–20	108·5	15–, 135·0
8–9–10	109·47	3–, 30·0	17–19–21	108·5	15–, 255·0
8–9–11		3–, 150·0	17–19–22	111·3	15–, 48·5
8–9–12		3–, −90·0	19–22–23	109·4	17–, 70·0
9–12–29		8–, 60·0	19–22–24	109·4	17–, 190·0
9–12–14		8–, −60·0	19–22–25	110·3	17, −56·0
9–12–13		8–, 180·0	22–25–26	109·47	19, 180·0
3–8–15	120·0	2–, 135·0	22–25–27	109·47	19, 300·0

* θ_{ABCD} is the 3–8–15–16 dihedral angle. The dihedral angle is defined in such a way that for A–B–C–D (where A is nearest the observer who is looking down the BC bond), θ is the angle (+ clockwise) between the projected bond AB and projected bond CD. The Set I, 0° configuration is given here. All other configurations are easily derived from this by simple changes of the dihedral-angles.

Table 2.   *Energies (in kcal and kJ) relative to the lowest energy configuration (Set I, 180°).*

θ^a	Set[b]I		Set[b]II		Set[b]III		θ^a	Set[b]IV	
	kcal	kJ	kcal	kJ	kcal	kJ		kcal	kJ
0	0·43	1·80	0·71	2·97	1·17	4·90	−90·0	90·5	378·6
60	13·22	55·31	13·48	56·40	8·90	37·23	−45·0	64·2	268·6
120	2·80	11·71	3·20	13·38	3·92	16·40	0·0	3·6	15·06
180	0·0	0·0	1·52	6·36	0·96	4·02	+45·0	10·33	43·22
240	2·14	8·95	3·62	15·14	4·23	17·69	+90·0	90·4	378·2
300	4·32	18·07	5·10	21·33	4·75	19·97			

(a) See definition in Table 1.   (b) defined in Text.

−90°.   In set II Cl_1 (with the corresponding hydrogen atoms) is rotated through 120° so as to point away from the ring.   This Cl_1 configuration is maintained for set III but the 3–8–9–12 dihedral angle is changed to −45°.   Finally in set IV the mustard group is arranged so as to assume maximum internal symmetry (Fig. 1c).   In this configuration c_2 and c_{12} point toward the ring and the two chlorine atoms point away from the ring. For sets I, II, III calculations were made for every 60° rotation (note the definition of θ in Fig. 1b) and in set IV for every 45°.   For the first three sets of configurations the results are essentially similar (see Table 2).   Noting that the 0° configuration is defined such that the plane given by atoms 3–8–9 is essentially perpendicular to the six-membered ring for these sets, we find that the energy minima occur at 0° and 180° with significant barriers at 60° and 300°.   The 0° minima is in keeping with the X-ray result; the 180° configuration would be expected to be close to the 0° configuration energetically, because of the very similar arrangement of the atoms.   For set IV only the 0°–45° configurations are of sufficiently low energy to be populated at room temperature.   These configurations are similar to the 0° configuration of the first three sets.   The lowest energy of set IV is 3·60 kcal (16·1 kJ) above the lowest energy of the first three sets.

The mechanistic argument for the design of cyclophosphamide was that the electronegative phosphoryl linkage should remove enough of the nitrogen electron density to decrease the probability of the formation of a three membered ring ion-intermediate thought to be formed on loss of Cl^-.   Calculations on normustine ($HN\text{-}(CH_2CH_2Cl)_2$) show that the nitrogen electron density falls to a small extent only, from an excess of 0·223 electrons in normustine to an excess of 0·185 electrons in the lowest energy conformation of cyclophosphamide.   Although this decrease is in the correct direction, its small size would suggest that some other mechanism could be responsible for deactivating the mustard part of the molecule.   It is interesting to note that both oxygens and the ring N could all possibly participate in the activation of the mustard linkage since many of the rotations bring the chlorine atoms fairly close to these electronegative atoms.

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