INVESTIGATION OF CONFORMATIONAL STATE OF MOLECULES OF

DIMEPHOSPHONE $H_3C-(C=O)CH_2-C(CH_3)_2-(P=O)(OCH_3)_2$ BY MEANS

OF VIBRATIONAL (IR, RAMAN) SPECTROSCOPY AND MOLECULAR MECHANICS

A. Kh. Plyamovatyi, I. I. Vandyukova,
R. R. Shagidullin, and A. O. Vizel'

On the basis of data obtained by vibrational spectroscopy and molecular mechanics, the molecules of dimephosphone are found to be conformationally inhomogeneous, representing a mixture of at least four spectrally distinguishable conformers.

Dimephosphone (DMP) is an antiacidotic organophosphorus pharmaceutical preparation with a broad spectrum of therapeutic applications [1, 2]. Since these applications may be governed by specific spatial positions of the functional groups, there is an urgent need to study the conformational behavior of the DMP molecules.

We have investigated the IR and Raman spectra of liquid samples of DMP, and also solutions in polar and nonpolar solvents MeCN and CCl_4 (concentration $C \approx 10^{-3}$ to 10^{-4} M, in order to eliminate intermolecular association). The behavior of vibration intensities has been studied over a range of temperature from $+28°C$ to $-98°C$, and also for liquid—crystal transitions. Analysis of the spectral information obtained in this work indicates conformational inhomogeneity of the molecules of this compound: Reversible changes are observed in the intensities of a number of vibrations when there are changes in the temperature or the polarity of the medium; it has also been found that a number of the frequencies are "frozen out" upon crystallization. The most informative frequency intervals proved to be 1750-1680, 1300-1200, 750-650, and 550-450 cm^{-1}, where these changes are particularly significant (Fig. 1).

Attention is directed to the doublet character of $\nu C=O$. The difference in frequencies (10 cm^{-1}) between its components remains unchanged by a change in the solvent polarity. In the more polar solvent (MeCN), there is a shift of the doublet and an increase in intensity of its low-frequency component (Fig. 1a). The shift of the doublet can be explained by interaction with the solvent (apparently dipole—dipole type interaction); the increase in intensity can be explained by occupancy of the more polar form (or of groups of conformers making a contribution to this component). A reverse change in intensity is observed when the temperature of liquid DMP is lowered. This may indicate that, in the liquid, the more polar conformers (or conformer) are also less thermodynamically favorable. The energy difference ΔH, which we have estimated from the Van't Hoff relationship (1) according to the peak intensities, assuming that the ratio of extinction coefficients is independent of temperature, is -0.1 kcal/mole

$$\ln \frac{A_1}{A_2} = -\frac{\Delta H}{RT} + const$$

(1)

A_1 and A_2 are the respective intensities of the high-frequency and low-frequency components.

Conclusions analogous to those described above can be drawn from an analysis of the behavior of the frequencies in the 1300-1200 cm^{-1} region, where the most intense vibration is that of $\nu P=O$ (Fig. 1b). For the bands at 660 and 533 cm^{-1}, the decrease in intensities as the temperature is lowered and the freezing of the bands upon crystallization indicate that these vibrations pertain to the thermodynamically less favorable forms (Figs. 1c and 1d).
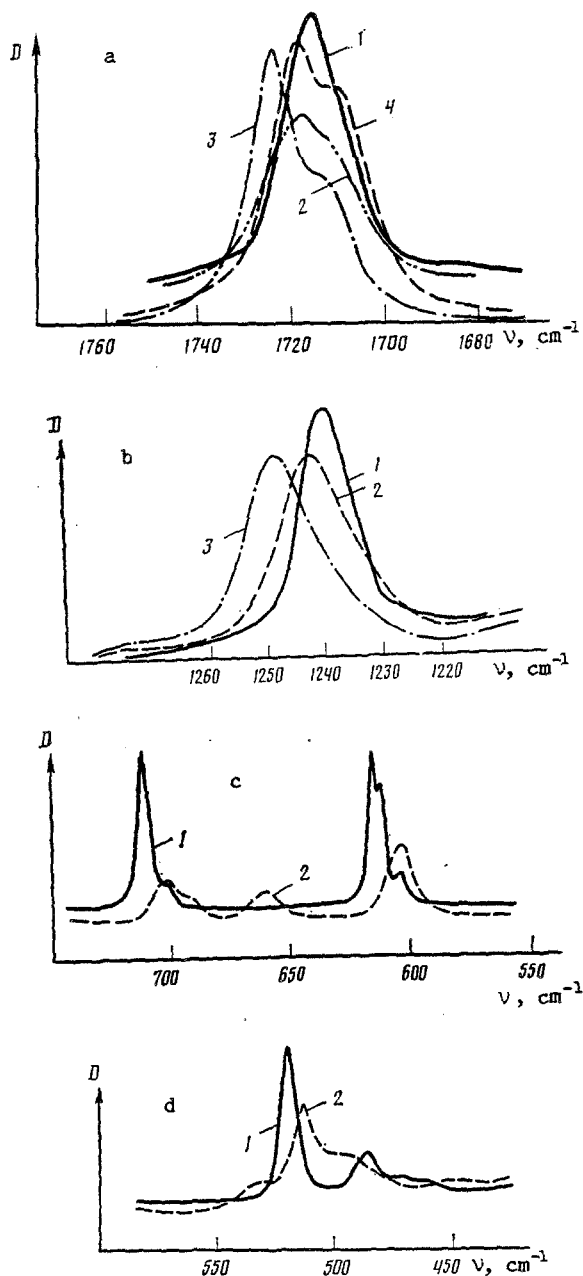
Fig. 1. IR spectra of DMP molecules (a-d) in liquid, crystal, and solvents: 1) crystal; 2) liquid; 3) solution in CCl_4; 4) solution in CH_3CN.

In order to relate the above-described experimental effects to the spatial structure of DMP, we investigated the conformational behavior of its molecules by methods of molecular mechanics, in a version that takes into account the interaction of unshared electron pairs [3].

The theoretically possible number of conformations, if we take into account the presence of torsion angles, each of which may assume three values, will be 3^5
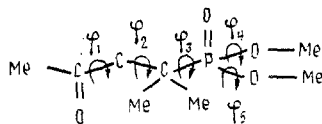
Conformer	φ_1	φ_2	φ_3	φ_4	φ_5	E	μ
1	−5	−179	−179	−34	64	0,1	6,3
2	−5	−179	−59	−34	64	0,0	4,2
3	−5	−179	−60	−64	34	0,0	3,9
4	−107	−179	−59	−34	64	0,6	6,4
5	−107	−179	−61	−64	34	0,6	6,3
6	−107	−178	−179	−34	64	0,8	4,3
7	−107	−178	60	−34	63	0,7	3,6
8	56	58	−64	64	−34	1,3	6,1
9	56	60	−62	34	−64	1,3	6,2
10	56	65	175	−34	64	1,8	3,4
11	59	63	56	−34	64	1,5	2,3
12	54	62	54	−64	34	1,5	2,2
13	−111	61	56	−61	36	1,4	5,1
14	−128	43	−63	64	−34	2,4	4,7
15	110	62	62	34	64	1,6	4,9

However, when we take into account degeneracy of the conformational space, the number of different conformations will be 122. In practice, it can be shown that not all of these conformations will be thermodynamically stable. The required bond lengths (calculated on the assumption of rigid bonds) and the initial values of the bond angles were taken from [3, 4]. The elastic constants of the bond angles, the potentials of nonvalence interactions, and the barriers to internal rotation were taken from [4, 5]. In this literature, where the calculational model was the same as that used here, no values were given for the parameters through which rotation around $(O)C-C_{sp_3}$ bonds could be described. For an adequate reproduction of the character of such rotation, it is necessary to use a torsion potential in the form

$$E_{tor} = 0.5\,V_1\,(1 - \cos 2\varphi_1) + 0.5V_2\,(1 - \cos 3\varphi_1) \qquad (2)$$

where φ_1 is the O=C-C-C dihedral angle; V_1 and V_2 are 1.13 and 1.11 kcal/mole, respectively. The derivation of this expression will be given in a separate publication.

The total energy of the molecule, following [3], was represented in the form

$$E = E_{ang} + E_{tor} + E_{coul} + E_{nval} \qquad (3)$$

where E_{ang}, E_{tor}, E_{coul}, and E_{nval} are the respective energies of deformation of bond angles and torsion angles, the interaction of unshared electron pairs, and nonvalence interactions.

In calculating the energies of the conformers, we carried out a minimization of (3) by the method of Davidon, Fletcher, and Powell [6] for five dihedral angles $\varphi_1-\varphi_5$ and 11 independent bond angles (two for the carbonyl carbon, two CCC angles in the cores of the molecule, five angles at the P atom, and two POC angles of the oxymethyl groups). With the aim of curtailing the number of variables, all angles in the Me groups were assumed to be tetrahedral, as were the CCMe angles. A feature that we found in the conformational behavior of DMP is the almost complete absence of any rotation around P—O bonds. In all of the stable conformers that we obtained, the angles φ_1 and φ_5 (O=P-O-Me) were either −30° and 64° or (symmetric relative to the plane passing through the atoms =O, P, C) −64° and 30° (Fig. 2).

The most probable conformers that we found and the characteristics of these conformers are listed in Table 1. Since the values found for the bond angles are very similar in all of the stable conformations, we will give average values here: CC*O 122.0°, CC*C 120.0°, CCP 114.0°, CP=O 110.9°, O=PO 116.0°, CCP 102.1° (the asterisk denotes a carbonyl C atom).

In evaluating the polarity of the conformations that have been found, we calculated dipole moments, using an additive vector scheme. The bond lengths required for this calculation were taken from [7]. The following values were found: C → O 1.74, C → C* 0.78, C → C 0.00, C → P 0.58, P → O 2.95, O → P 0.75, C → O 0.99, H → C 0.28.
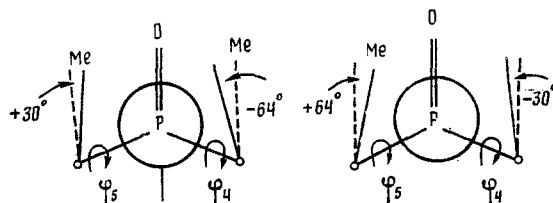
Fig. 2. Orientation of oxymethyl groups in stable conformations.

TABLE 2. Normal Vibration Frequencies Calculated for DMP Conformers That Have Been Found (values of νP—C for conformers 8-15 are not characteristic and are mixed with other vibrations)

Conformer	νC=O		νP=O		νP—C		δOCC				
1	1728		1249		733				602		491
2	1728			1244	730				603		488
3	1727			1243	731				603		487
4		1721	1250			717			588		490
5		1720	1250			717			589		492
6		1721	1250			718			589		492
7		1721	1250			717			588		490
8		1717		1239			680			551	
9		1717		1239			681			557	
10	1723		1249				679	596			
11	1723		1254				680	593			
12	1723		1254				680	593			
13		1721	1254				681	589			491
14		1719	1250	1239			681	592		519	
15		1720	1250				681	591			492
Experiment	1725	1712	1246	1238	701	690	660	610	600	533	500

Results from the estimate of polarity are also given in Table 1.

It was noted above that the experimental data permit classification of all conformers into two groups according to polarity. It can be seen clearly that all of the conformers listed in Table 1 can indeed be divided into two groups. The first group consists of forms with dipole moments of 5-6 D; the second group (less polar) consists of forms with dipole moments 2-4 D. However, such a division would be merely a formal classification, possibly with no real meaning. It would be important for the two groups of conformers to have different spectral characteristics as well, governed in particular by the behavior of the νC=O doublet. Therefore, within the framework of the same theoretical approach (method of molecular mechanics), for each of the conformers listed in Table 1, we have calculated its vibrational spectrum. To do this, we also needed the elastic constants of the bonds (K, kcal/mole·Å²) and their "ideal" values (l_0, Å). We have assumed the following:

Bond	$K/10^2$	l_0
P=O	12.816	1.430
C=O	14.400	1.200
P–C	4.534	1.800
C–C	4.000	1.355
C–H	5.899	1.040

The calculated vibration frequencies for a number of spectral regions are listed in Table 2. As was noted previously, one of the most informative vibrations in the experimental spectrum is that at 660 cm^{-1}, which decreases in intensity with decreasing temperature, disappearing upon crystallization. It can be seen from Table 2 that this vibration can come only from conformers having $\varphi_2 \sim 60°$ (forms 8-15). In a manner similar to that for the 660 cm^{-1} frequency, the vibration at 533 cm^{-1} also disappears upon crystallization, and thus pertains to that same (or those same) less favorable form. It follows from Table 2 that only conformers 8, 9, and 14 have a frequency in the 500-590 cm^{-1} region (551, 557, and 519 cm^{-1}, respectively). The νP=O region makes it possible to choose among these conformations. Here, in a polar solvent, the intensity of the low-frequency component increases; i.e., it is due to the polar form. According to the calculation of frequencies (Table 2), the three conformers under consideration can make a contribution to the low-frequency component of νP=O; however, in the first place, conformer 14 simultaneously
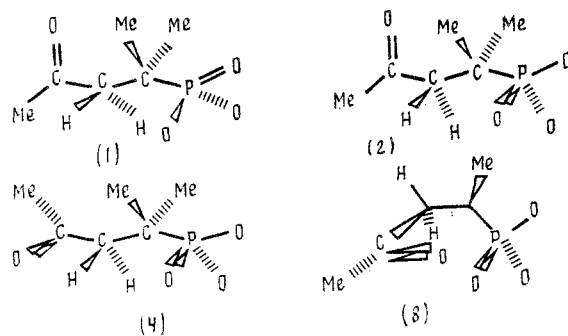
Fig. 3. Representation of most probable conformers in DMP molecule.

makes a contribution to the high-frequency component; and in the second place, it is less polar and has a high energy (Table 1). In view of these considerations, we tend to give the preference to forms 8 and 9. Unfortunately, as can be seen from Table 2, there are no more vibrations that would pertain to only the less favorable form and are not mixed with the frequencies of other conformers. Thus, a conformer (or conformers) from the group 1-7 may remain in the crystal. Let us now examine these conformers.

We will turn our attention to the experimental frequencies near 700 cm^{-1}. Here (Fig. 1c), we observe a distinct doublet at 701/690 cm^{-1}, for which the high-frequency component increases rapidly in intensity as the sample is cooled. Upon crystallization, the doublet is shifted by ~10 cm^{-1}. It follows from Table 2 that the presence of these vibrations in this particular region can be explained only by coexistence of at least two conformers; i.e., it is necessary to "break up" the group of conformers 1-7 into two subgroups. The first consists of forms 1-3, which have a higher frequency in the region under consideration (~700 cm^{-1}); the second subgroup consists of forms 4-7. We can arrive at the same conclusions by examining the region ~600 cm^{-1}. Here we observe in the liquid a single band, but we should expect on the basis of the calculation two vibrations differing by ~10 cm^{-1}. And in fact, as the sample is cooled, the intensity of this band increases (probably due to conformers 8 and 9), and it becomes considerably more asymmetric. Upon crystallization, there is a high-frequency shift (~10 cm^{-1}), and the two components are rather clearly isolated. Here we observe splitting of the high-frequency component (Fig. 1c). Thus, our results indicate that an equilibrium among at least three forms is observed in the liquid, and at least two of them remain in the crystal. Since the intensity of the vibrations at 711 and 615 cm^{-1} is higher than that of the vibrations of 701 and 604 cm^{-1} (Fig. 1c), the most highly populated subgroups is apparently 1-3. From this it also follows that the $\nu C=O$ vibration observed in the crystal at 1715 cm^{-1} is a slightly shifted high-frequency component of the "liquid" doublet (in the liquid, this frequency is 1719 cm^{-1}). The calculations (Table 2) transmit quite well the fact that we should expect in the liquid only two $\nu C=O$ frequencies, with conformers 8, 9, and 4-7 contributing to the low-frequency component. Conformers 4-7 cannot be resolved spectrally (in any case, in the mid-IR region); moreover, these forms are close in energy. The same remarks can be made with respect to the conformers of subgroup 1-3. However, since we have noted experimentally the high polarity of forms contributing to the low-frequency component of $\nu C=O$, the preference in group 4-7 should probably be given to conformers 4 and 5, and from the first subgroup to all forms, since the net dipole moment of this subgroup will be lower. Since conformers 2 and 3 have practically identical moments (~4 D), and since they have equal energies and are spectrally similar, we will not include both of these conformers in our subsequent examination, rather considering only conformer 2, with a doubling of its statistical weight. On the basis of the same considerations, we will proceed analogously for conformers 4 and 5 and for 8 and 9, here considering only 4 and 8. As discussed previously in this paper, on the basis of the $\nu C=O$ bands and Eq. (1), we had obtained an estimate of the difference between the energies of the conformers, ~-0.1 kcal/mole. This value represents the difference between the mean energy of conformers contributing to the band A_1 and the mean energy of conformers responsible for vibration A_2. According to [8], this can be expressed by the formula
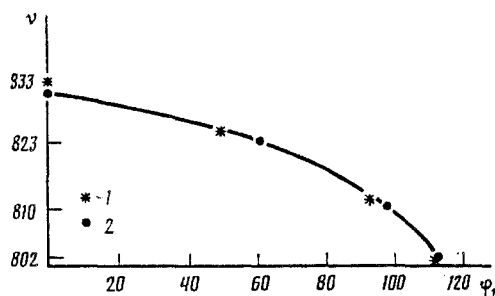
Fig. 4. Stretching vibration νC—C as a function of mutual orientation of C=O and C—C bonds: 1) experimental; 2) calculated frequencies.

$$\Delta H_m = \frac{\sum_i E_i g_i \exp(-E_i/RT)}{\sum_i g_i \exp(-E_i/RT)} - \frac{\sum_j E_j g_j \exp(-E_j/RT)}{\sum_j g_j \exp(-E_j/RT)} \qquad (4)$$

where the summation in the first fraction is made for conformers 1 and 2, which contribute to A_1, and the summation in the second fraction for 4 and 8; g is the statistical weight; E is the energy of the conformers.

If we make use of the energies listed in Table 1, we obtain $\Delta H_m \approx -0.7$ kcal/mole, which is in poor agreement with the estimate given above (the calculations of energies were performed with a dielectric constant of 1.0).

Thus, what is probably realized in liquid DMP is an equilibrium of four conformers 1, 2, 4, and 8 (Fig. 3). Upon crystallization, conformer 8 is frozen out. In the crystals that we obtained, a mixture of conformers is realized, with form 1 and/or 2 predominating; form 4 is present in smaller amounts. It is impossible on the basis of the spectral data to choose between conformers 1 and 2 for the most highly populated form in the crystal.

From Fig. 3, where we show schematically the most probable conformers, it can be seen that there is a change in the mutual positions of the carbonyl bond C=O and the phosphoryl bond P=O. Since these bonds have the largest dipole moments, they are probably responsible for the biological activity of the DMP molecule, through bonding with the target molecules; here, conformers 4 and 8 can act as bidentate ligands
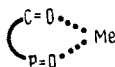
(in conformer 1, the Me groups will probably not favor such action). Since the distance between the O atoms of the carbonyl and phosphoryl groups in conformers 4 and 8 are different ($r_4 \approx 5.15$, $r_8 \approx 3.42$, respectively), we can also assume that they may interact with different target-objects.

In conclusion, let us also note the high sensitivity of the νC—C vibration to the dihedral angle φ_1 (Fig. 4). Since this vibration is quite intense, the indicated frequency can be used as an analytical frequency for evaluating the orientation of the carbonyl group.

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