CONFORMATIONAL DEPENDENCE OF SOLVATION ENERGY OF PHOSPHATES

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Conformational dependence of solvation energy has been calculated for dimethyl phosphate, its monoanion and ion pair with the proton considering rotation about P—O bonds in the molecules. The solvent (water) effect has been expressed using the continuous model according to Sinanoglu. Contribution of individual terms (electrostatic, dispersion and cavity) of the solvation energy in the stabilization of individual conformers has been analyzed. Some of methodical problems of the calculation of solvation energy have been discussed and particularly the inevitability of reliable determination of torsional dependence of molecular volume has been stressed. A comparison of the three molecules has shown that different character of the solvation energy dependences is due to the electrostatic term and is connected with orientation of the group dipole moment of the central PO_2 group in the individual molecules.

Recently considerable attention was paid to interpretation of solvent effects on properties of molecules especially with respect to their conformations. It is particularly in biology where small differences in spatial structure due to solvent can result in considerable changes of biological functions of the molecules. Theoretical descriptions of influence of medium on conformation usually start from some of two approximative models: microscopic representation of solvent (the nearest solvent molecules only being considered) or macroscopic representation of solvent as a continuum. The both approximations have their particular advantages and are developed simultaneously in literature[1-3].

In a number of biomolecules phosphate group plays an important role. It forms *e.g.* connecting bridge between nucleosides in nucleic acids, and it is found in phospholipid components of biological membranes. The preferred spatial arrangement of an isolated phosphate group was investigated many times (especially the simplest model compound – dimethylphosphate monoanion) by means of molecular-mechanical and quantum-chemical methods at various approximation levels[4-9]. From the results it follows that the most stable are *gauche*-conformations as (*sc*, *sc*), (*sc*, *ap*) *etc.* So far all attempts to describe the solvent effects on phosphate conformations[10-13] started from the microscopic (supermolecular) model of solvation of phosphates by one or more water molecules. We considered it useful to treat the problem also by the complementary continuous model and we used the method by Sinanoglu[14]. First of all we were interested in detailed analysis of influence of solvation energy and its individual contributions on conformation equilibrium of isolated phosphate molecules and in the extent to which these effects are affected by ionization and by the presence of counter-ions. We also pointed out at the existing limitations of the present theoretical approach in the quantitative prediction of conformational structure of phosphates in solution. Finally we discussed the role of solvation energy in manifestation of anomeric effect[15,16] in phosphate segment of the bonds and compared it with the findings concerning the cognate acetal bond segment[17].

RESULTS AND DISCUSSION

The calculation model and method. We investigated the conformational stability of dimethyl phosphate (DMPH) CH_3—O—POOH—O—CH_3, its monoanion (DMP^-) and ion pair (DMP^-H^+) in aqueous solutions depending on rotation about the central P—O bonds characterized by the angles ω and ω' (Fig. 1). The torsion angles have the values 180, ±60 and 0° for antiperiplanar (*ap*), synclinal (±*sc*) (also denoted as *gauche*) and synperiplanar (*sp*) positions, respectively. In the calculations rigid geometry of the molecules was presumed with the same parameters as in our previous report dealing with the isolated DMP^- molecule[9]. The methyl groups were in the most stable *staggered* position. The chosen coordinate system has its origin in the phosphorus atom, and the axes are defined by intersections of the perpendicular planes crossing the atoms O_a—P—O_a and C—O—P—O—C (in all-*ap*, zig-zag arrangement). The individual conformations characterized by the angles ω, ω' are denoted as (ω, ω') *e.g.* (*ap*, *ap*) for the conformation given in Fig. 1. For position of the acid hydrogen in DMPH we considered the value 0·10 nm for the O_a—H bond length, its localization being in *xz* plane in *ap* conformation with respect to the opposite P—O_a bond. In the intimate ion pair DMP^-H^+ the proton was located at a distance 0·225 nm from the phosphorus atom symmetrically to DMP^- in the negative direction of *x* axis (Fig. 1).

The dipole moments and charge distributions were calculated for all the three molecules by the standard CNDO/2 method[18] with *sp* and *spd* basic set of AO's at phosphorus, the values being partially given in ref.[9]. Similar to the case[9] of DMP^-, also here in the case of DMP^-H^+ and DMPH potential energy of the isolated molecules was calculated on the basis of molecular-mechanical method with modified expression of the electrostatic term into which the dipolar interactions of lone electron pairs[19] were involved, too.

To express the influence of medium (water) on conformational equilibrium of the phosphates, we used the continuous model by Sinanoglu[14,20,21] which proved competent earlier in calculation energy of acetals[17]. This approach simply presumes that energy of a solute in a solvent can be expressed as a sum of potential energy of the isolated molecule (E_{isol}) and contribution of solute–solvent interactions (E_{solv}) which is composed of an electrostatic, a dispersion and a cavity terms.

$$E = E_{isol} + E_{solv} = E_{isol} + E_{el} + E_{disp} + E_{cav} \qquad (1)$$

Such expression of solvation energy considers the specific interactions between solute and solvent as conformationally independent. The electrostatic solute–solvent interactions are given, on the basis of the reaction field theory, as the sum[14,20-22]

$$E_{el} = E_{ch} + E_{dip} + E_{qu} , \qquad (2)$$

where the individual terms at the right-hand side express interaction energy of a point charge[23] (the Born term), a point dipole[20,22] (the Onsager term), and a point quadrupole[22] located in the centre of a spherical cavity having the radius a and permittivity equal to unity with the field induced in an infinite dielectric of permittivity ε into which the spherical cavity is immersed. Calculation of the contribution of the dispersion interactions is based on determination of effective interaction potential for the solute molecules surrounded by the solvent molecules[14,21,24]. The last term at the right-hand side of Eq. (*1*), E_{cav}, represents the energy needed for formation of a spherical cavity in the solvent, the magnitude of the cavity being sufficient for a solute molecule to be placed inside. More detailed description of the analytical expressions as well as the values of the parameters necessary for calculation of the terms E_{disp} and E_{cav} (water as the solvent) can be found in literature[14,17,20,21,24].

All the three terms of solvation energy at the right-hand side of Eq. (*1*) depend on size of the cavity, *i.e.* on the molecular volume. For calculations of the changes of molecular volume due to rotation we used the procedure by Beveridge and coworkers[20]. The solute molecule is approximated by a right parallelepiped whose dimensions are determined by extreme positions of the atoms in the directions of individual axes plus 0·2 nm. The right parallelepided is substituted by a sphere of the same volume, and radius of this sphere represents the cavity radius for the given solute.

Conformational dependence of solvation energy. Variation of the angles ω and ω' by 10° gave conformational maps of solvation energies $E_{solv}(\omega, \omega')$ which on superposition with the maps of potential energy of the isolated molecules $E_{isol}(\omega, \omega')$ enable to get a picture of conformational stability of phosphates in aqueous solutions. Due to not quite satisfactory reliability of the procedures used so far for quantitative description of solvation (hydration) energy, we shall limit ourselves rather to qualitative evaluation of the calculations. We shall analyze consecutively the conformational

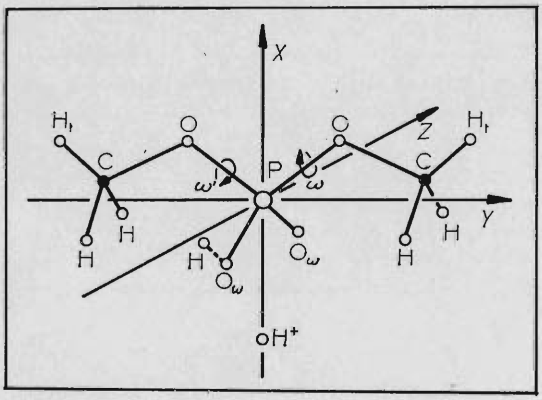


FIG. 1

Schematic representation of the chosen coordinate system for (*ap*, *ap*) conformation of DMP^-, DMPH and DMP^-H^+

dependences of the individual E_{solv} terms and show a number of methodical problems encountered in the calculation. For detailed analysis of conformation dependences of the individual terms of Eq. (*1*) the sections through the conformational map at $\omega' = 180°$ and $\omega' = 60°$ are especially useful. All significant conformational minima of the phosphate segment of bonds as (*sc*, *sc*), (*ap*, *sc*) and (*ap*, *ap*) and their symmetrical positions lie at these sections or close to them. Comparison of the calculation results in the series of molecules DMPH, DMP^-H^+ and DMP^- with increasing ionic character helps to reveal the extent to which the solvation properties of the phosphates are affected by degree of dissociation. Although the DMPH molecule is probably ionized to a high degree in real aqueous solutions, it can serve as a suitable reference molecule in the calculations.

Electrostatic term E_{el}. This contribution to solvation energy represents a so called dielectric solvent effect, the interactions with water being reduced to mere interactions of the solute with a dielectric having a high value of relative permittivity. For electroneutral molecules the Eq. (*2*) according to Abraham[22] reads as follows

$$E_{\mathrm{el}} = -\frac{\mu^2}{a^3} \frac{x}{(1 - 2\alpha x)\, 4\pi\varepsilon_0} - \frac{hx}{2a^5(5 - x)\, 4\pi\varepsilon_0}, \qquad (3)$$

where ε_0 means permittivity of vacuum, μ stands for permanent dipole moment of the solute, h is function of the individual components of the quadrupole[22], x equals to the ratio $(\varepsilon - 1)/(2\varepsilon + 1)$ (approximately 0·5 for water), and α is given as $(n^2 - 1)/(n^2 + 2)$ where n is refractive index of the solute. The value $n = 1{\cdot}4036$ of trimethyl phosphate[25] was used for all the three molecules, as no other values are available.

From Eq. (*3*) it follows that the conformational dependence of the electrostatic contribution depends on the variation of dipole moment and size of the cavity during rotation about the O–P bonds. Fig. 2 gives the dependences of the cavity radius a in all the three molecules studied for the sections $\omega' = 180°$ and 60°, respectively. It can be seen that the phosphates assume the minimum volume in the (*ap*, *ap*) conformation.

Fig. 3*a* gives the torsional dependence of the dipole moment μ of DMP^- at $\omega' = 180°$ obtained by the CNDO/2 method using the *spd* basic set of AO's at phosphorus. An analogous dependence also resulted, if the *sp* valence orbitals only were considered in the CNDO/2 method. For the other two molecules the torsional dependences of the dipole moments were computed only indirectly due to lengthy convergency of the SCF procedure. The CNDO/2 charge distribution modified by a set of charges representing the lone electron pairs[19] calculated for the (*ap*, *ap*) conformation of DMP^-H^+ and DMPH was assumed independent of rotation and was used for calculation of torsional dependence of dipole moment. The results for the section $\omega' = 180°$ are given in Fig. 3*a* where it can be seen that values of the dipole

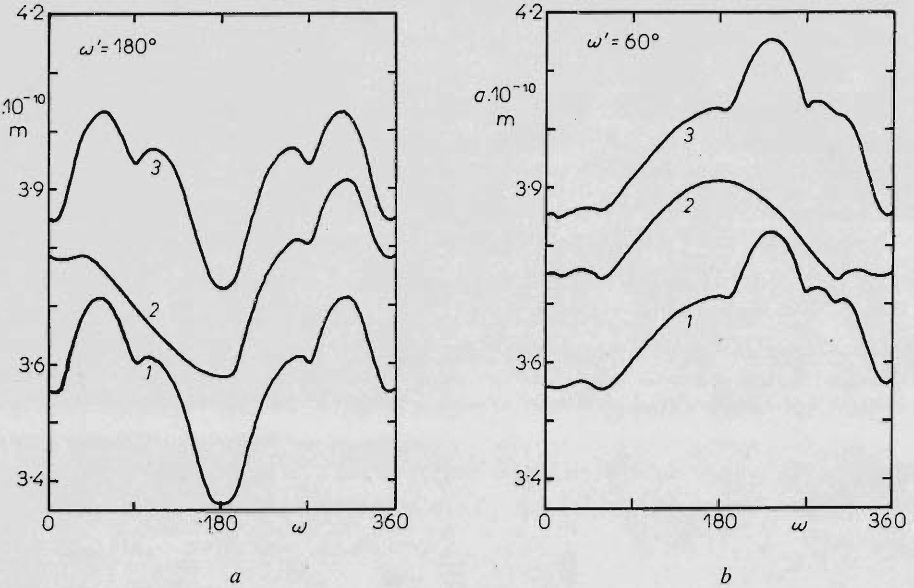


FIG. 2

Dependence of radius of spherical cavity on angle ω at constant value of angle ω' *a* $\omega' = 180°$; *b* $\omega' = 60°$. DMP^-: curve *1*, DMPH: *2* and DMP^-H^+: *3*

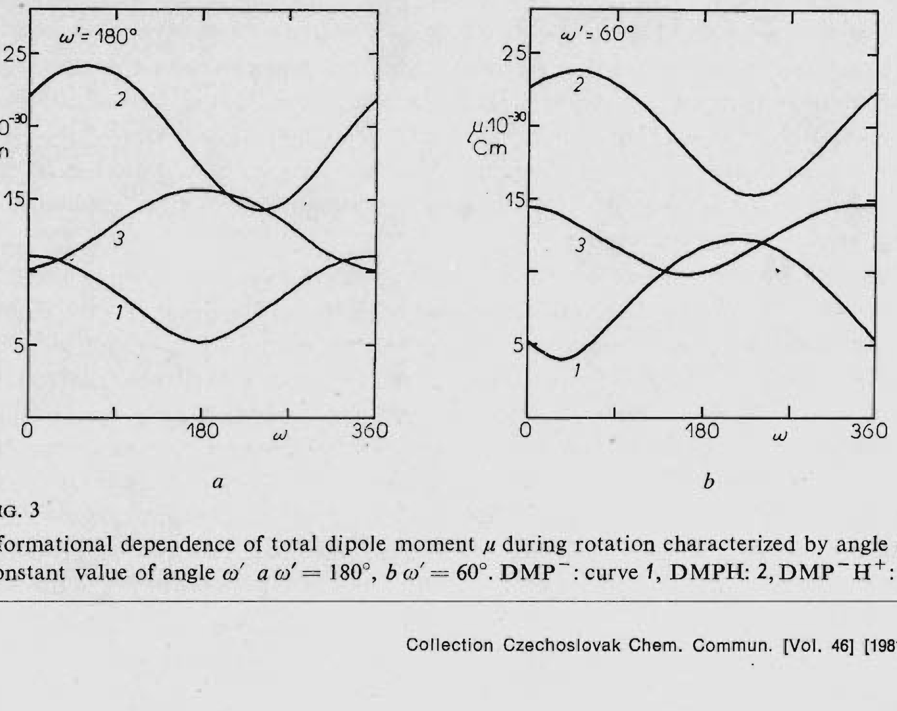


FIG. 3

Conformational dependence of total dipole moment μ during rotation characterized by angle ω at constant value of angle ω' *a* $\omega' = 180°$, *b* $\omega' = 60°$. DMP^-: curve *1*, DMPH: *2*, DMP^-H^+: *3* moments as well as their torsional dependences are markedly influenced by ionic character of the phosphates. In similar way, on the basis of the CNDO/2 charge distribution modified by the presence of lone electron pairs[19] we also obtained (for all the three molecules) the variation of the dipole moments at $\omega' = 60°$ (Fig. 3*b*) as well as the quadrupole function *h* involved in the last term at the right-hand side of Eq.(*3*).

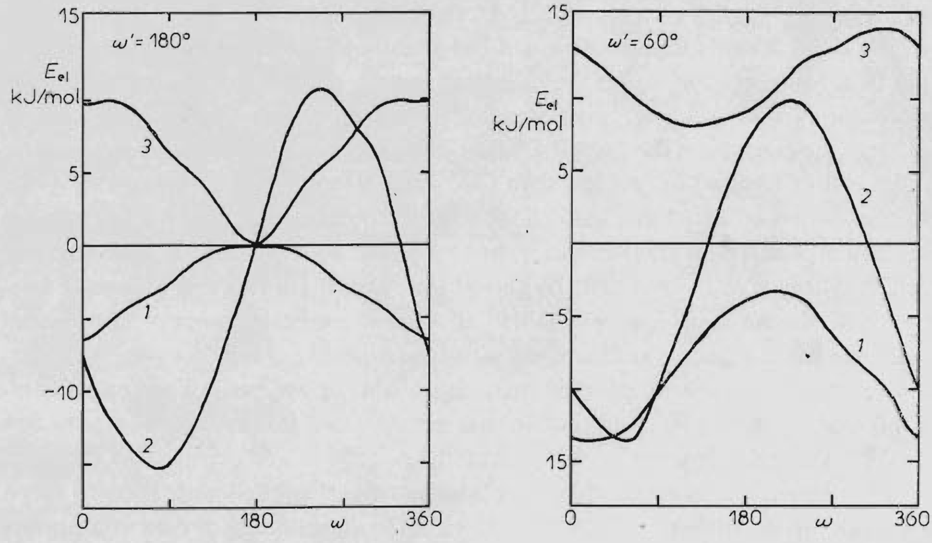
As in ref.[20], we neglected conformational dependence of the monopole term in calculation of E_{el} according to Eq. (*3*), and we focused our attention on comparison of the dipole terms of all three molecules. The monopole term (proportional to $-Q^2/a$) has the greatest absolute value out of all the contributions to E_{el} in the case of DMP^-. Its conformational dependence, which is given by the conformational variation of the cavity radius, is, however, relatively unreliable. It can be presumed that in all the three molecules studied the dipole term will represent the determining contribution to the conformational dependence of the E_{el} term due to great changes of the dipole moment with conformation (Fig. 3). The different conformational dependences of dipole moment result in different effects of the electrostatic contribution to the conformational stability in DMP^-, DMPH and DMP^-H^+. Another reason of neglection of the monopole contribution consists in an artificial overestimation of significance of this term, if the whole negative charge *Q* is placed (in accordance with the reaction field theory) in the centre of the cavity, although in fact it is delocalized over the whole molecule.

The calculated dielectric solvent effect is given in Fig. 4 for the sections $\omega' = 180°$ and 60° for all the three molecules. The calculation showed that in the molecules studied the quadrupole term contributed but slightly to the overall dielectric solvent effect. According to expectation the dielectric solvent effect is manifested in that the conformations having higher dipole moment will be more stabilised in aqueous solutions. For example in the case of DMP^- in the section $\omega' = 180°$ it means greater stabilization of (*ap*, *sc*) or (*ap*, *sp*) than (*ap*, *ap*) conformation. Comparison of the dielectric solvent effect from Fig. 4 shows clearly considerable sensitivity of relative stabilization of the individual conformations in water to the presence and character of acidic hydrogen in the molecule of phosphates. In this context it is especially interesting that the intimate ion pair DMP^-H^+ shows an entirely opposite torsional dependence of the E_{el} term as compared with the remaining two molecules.

A simplified explanation of this difference is possible on the basis of mutual orientation of the group dipole moments in the phosphates. In (*ap*, *ap*) conformation of DMP^- the both group moments of methoxy groups are oriented in direction of *x* axis, whereas the moment of PO_2^- group has an antiparallel orientation to them. The overall dipole moment of DMP^- is given by the resultant of these two opposite effects. Rotation of one methoxy group by an angle ω (the angle ω' being equal to 180°) results in diminishing of the mentioned mutual compensation, and μ of DMP^- increases (Fig. 3). A different situation is encountered with the DMP^-H^+ molecule. Due to the presence of the proton the group dipole of the $PO_2^-H^+$ group is oriented along x axis, so that in (ap, ap) conformation of this molecule all the three group moments are roughly parallel, and μ of DMP^-H^+ reaches the maximum value (Fig. 3). Thus it can be seen that even the calculation of the conformational dependences of the dipole moment type $\mu(\omega, \omega')$ would give a qualitatively correct estimate of the dielectric solvent effect of all the three phosphate molecules.

The relatively abrupt changes of the E_{el} term of the neutral DMPH molecule can be connected with the fixed position of the acidic hydrogen atom in the calculation. A better approximation would involve varying hydrogen position for varying conformation of the basic segment.

The quantum-chemically calculated dipole moment is generally composed of a number of contributions, *e.g.* (in the case of the standard CNDO/2 method) of that of the dipole moment of net charges at the atoms μ_{ch} and that of atomic hybridization dipole moments[18] μ_h. Our calculations showed unambiguously that also in the case of the phosphates the value μ_h contributes significantly to the overall dipole moment of the molecule (μ) and affects markedly its torsion dependence, too. For illustration we give the values of the total dipole moment and its contributions in two conformations of DMP^-. In the (ap, ap) conformation their values are following: $\mu = 5{\cdot}07$, $\mu_{ch} = 1{\cdot}57$, $\mu_h = 3{\cdot}50$; in the (ap, sc) conformation: $\mu = 9{\cdot}39$, $\mu_{ch} = 1{\cdot}57$, $\mu_h = 8{\cdot}12$ (all values in mC . 10^{30}). We have already pointed out that the contribu-



a *b*

FIG. 4

Sections through conformational maps $E_{el}(\omega, \omega')$ of dielectric solvent effect for $\omega' = 180°$ *a* and $\omega' = 60°$ *b* DMP^-: curve *1*, DMPH: *2*, and DMP^-H^+: *3* tion of hybridization dipole moments must inevitably be considered in calculation of intramolecular electrostatic interactions in conformational analysis[26]. Also in the present case it can be emphasized that neglection of contribution of the atomic hybridization dipole moments μ_h (which are due, first of all, to the presence of lone electron pairs at the atoms) would lead to underestimation of the dielectric solvent effect and to its incorrect conformational dependence. The failure of the solvation method[28] to predict the dielectric solvent effect of DMP^- and cognate molecules can also be explained by neglection of the contribution of μ_h (ref.[27]).

Calculation of dielectric solvent effect of phosphates is affected to some extent also by not quite satisfactory prediction of charge distribution and dipole moments by the quantum-chemical methods. The results depend on the method used, on the magnitude of base in *ab initio* methods, and on parametrization method in semiempirical procedures, a particularly important fact being the inclusion or non-inclusion of *d* atomic orbitals in the calculation. In the latter case the calculated charge distribution seems to show exaggerated polarity.

When discussing the electrostatic contribution to the solvation energy it must be noted that generally only the first non-zero multipole moment of the molecule is independent of choice of the coordinate system. In our case it means that the dipole moment of DMP^-, the quadrupole moment of the other molecules, and all higher moments will depend on the choice of coordinate system. Therefore, all our calculations are related to the coordinate system given in Fig. 1. Therefrom follows a frequently unnoticed fact that the E_{el} term and the whole solvation energy depend on the choice of coordinate system. However, this fact is less disagreable in calculations of conformational energies in solution with the aim of relative comparison of the solvation energy values.

Calculation of electrostatic contribution in the reaction field theory is also connected with methodical problems due to choice of the cavity for the solute. Even the estimate of magnitude and shape of the cavity is considerably arbitrary[29,30], the determination of the conformational dependence of the cavity volume being still less clear. The used calculation procedure[20] probably overestimates considerably the conformational changes of the radius *a* of spherical cavity. Although the calculation method of magnitude and conformational dependence of the cavity radius also effects the term E_{el}, a far greater is its influence of the other two terms of Eq. (*3*), *i.e.* the dispersion interactions and cavity term which depend critically on the cavity volume and surface, respectively.

The term E_{disp}. This term involves the van der Walls attractive and repulsive forces between solute and solvent. Calculation of its value is not yet satisfactorily mastered and is considered to be the least reliable of all contributions to the solvation energy. Its conformational dependence represents a complex function of solute volume changes during rotation, because this quantity affects both direct and indirect several parameters in calculation of the E_{disp} term[14,20,21,24]. Fig. 5 gives the torsional dependence of E_{disp} for the DMP$^-$ molecule as an illustrative example of the changes due to this contribution. For the section $\omega' = 180°$, the E_{disp} term stabilizes the sc^+ and sc^- conformations of the molecules as compared with the *ap* conformation. The E_{disp} curves of the other two phosphates show only small qualitative difference. The small differences in their course only reflect differences in the torsional dependence of molecular volume of the phosphates (Fig. 2), because the remaining parameters used in calculation of the E_{disp} contribution were identical for all the three molecules.

Energy of cavity formation E_{cav}. This contribution is determined by a combination of macroscopic properties of the solvent, as *e.g.* surface tension, and "microscopic" molecular volume. At the same time it is presumed that molecular volume only depends on conformation, the macroscopic parameters being considered conformational-independent. This presumption results in that the conformational dependence of the E_{cav} term follows directly the changes of the cavity radius a during internal rotation. This fact is also confirmed by comparison of the DMP$^-$ curve for E_{cav} in Fig. 5 with the variation of the radius a in Fig. 2. Also it can be seen that the E_{cav} dependences represent an approximate reduced mirror image of the curves for the E_{disp} term. Thus the contributions of these two terms to the overall solvation energy are mutually compensated to some extent. We suppose that this effect of mutual compensation is even greater in reality than in Fig. 5. The reason is in the above-mentioned overestimation of the conformational changes of the cavity radius and hence also overestimation of conformational dependence of cavity energy. An analogous mutually opposite conformational dependence of these two terms was also observed in other sections ω' of the conformational maps of solvation energy $E_{\mathrm{solv}}(\omega, \omega')$.

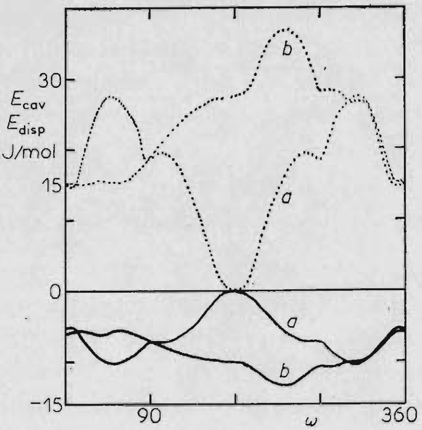


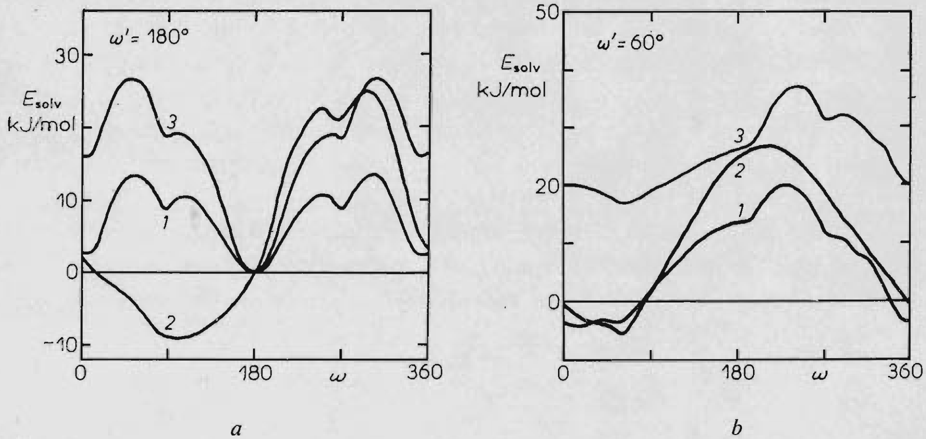
FIG. 5

Sections through conformational maps (ω, ω') for contributions of E_{disp} (———) and E_{cav} (·······) to solvation energy at $\omega' = 180°$ *a* and $\omega' = 60°$ *b* for DMP$^-$

The overall solvation energy E_{solv}. The resultant map of conformational dependence of solvation energy $E_{solv}(\omega, \omega')$ of the individual phosphates is obtained by summing all the three contributions E_{el}, E_{disp} and E_{cav}. We have already mentioned that this sum combines a relatively reliable determination of the dielectric solvent effect with the less reliable estimates of the other two terms in which critical role is played by the torsion dependence of molecular volume. Fortunately, the conformation dependences of these two contributions are mutually compensated to considerable extent. Out of the resulting map $E_{solv}(\omega, \omega')$, Fig. 6 only gives sections for some preferred ω' values. Comparison with Fig. 4 shows that differences in solvation energies between the individual phosphates are due predominantly to the electrostatic dipolar contribution.

With respect to complexity of the problem and to the mentioned approximations in the calculation method it is impossible to attach a great importance to the concrete numerical values. However, the calculation should be correct in qualitative expression of differences between the three types of phosphates with respect to stabilization of their individual conformations by the presence of water. It is seen that for DMP^- aqueous medium stabilizes the (*ap*, *ap*) and (*sc*, *sc*) conformations in roughly the same way. With the neutral molecule the most stabilized structures are close to the (*sc*, *sc*) and (*sc*, *ap*) conformations. However, in the case of the ion pair the (*ap*, *ap*) rotational isomer only is markedly stabilized by water medium.

The conformational dependences of solvation energy of the model phosphates are used in another study[31] for discussion of conformational structure of biological



a *b*

FIG. 6

Sections through conformational maps $E_{solv}(\omega, \omega')$ of total solvation energy for $\omega' = 180°$ *a* and $\omega' = 60°$ *b* DMP^-: curve *1*, DMPH: *2* and DMP^-H^+: *3* phosphates in solution and in crystalline state. A critical analysis of available calculations[31] showed that even for the isolated molecule DMP$^-$ there exists a considerable discrepancy in determination of order of stable conformations and conformational energy values depending on the calculation method used. Distinct conformational dependences of solvation energy according to Fig. 6 present a convincing support of the statement that the frequently used comparisons of calculations concerning isolated molecules with experimental data for solutions or crystals are of little practical importance.

From experimental and theoretical results it follows[4-9] that phosphates can be ranged among the molecules showing generalized anomeric effect[15,16], *i.e.* they tend to stabilize the *sc* conformation as compared with the *ap* conformation. The phosphate segment of bonds is very similar structurally to the acetal segment, and, therefore, it is not surprising that also conformational properties of the both segments were found to be similar. In the case of acetals we stated[17] that classification of molecules by the presence or absence of anomeric effect also depends on medium. The distinct conformational dependence of solvation energy in phosphates (Fig. 6) only brings another evidence that *sc* position originally preferred from the intramolecular viewpoint can be suppresed by environmental factors. Furthermore it was shown that with phosphates the environmental influence on anomeric effect depends greatly on ionic character of the molecule. The highest preference of the (*ap*, *ap*) conformation is attained in the intimate ion pair DMP$^-$H$^+$.

The distinct stabilization effect of the (*ap*, *ap*) structure of the ionic pair represents the most important feature in the comparison of solvation energy of phosphates. The supermolecular calculations[10] indicated influence of water molecules in surroundings of DMP$^-$ on relative stabilization of (*ap*, *ap*) conformation with respect to (*ac*, *sc*) (as compared with the isolated molecule). Our results confirm this fact and indicate that such effect should be even more distinct, if the presence of the counter-ion is taken into account. In biological structures containing phosphate segment the role of counter-ion is played by the proton and/or alkali cations in aqueous media. Within the method used for calculation of electrostatic interactions in solvation energy the chemical identity of cation is not substantial, only the dipole formed by the cation and PO_2^- being important. Thus it can be supposed that the results obtained for the DMP$^-$H$^+$ pair could qualitatively express the typical features of conformational dependence of solvation energy for phosphate ion pairs containing alkali cations.

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