Theoret. Chim. Acta (Berl.) 50, 169–179 (1978)

THEORETICA CHIMICA ACTA

Conformational Analysis of Dimethylphosphate with Quantum-Mechanical and Classical Methods

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In order to shed light on the conformational behavior of polynucleotide chains, and in particular to clarify the origins of the barriers to internal rotation in the phosphodiester linkage, we computed, with a quantum-mechanical *ab initio* procedure, the energies associated to 86 combinations of the two torsion angles in the dimethylphosphate anion $(CH_3O)_2PO_2^-$, and then we sought for an analytical expression apt to reproduce these energies with the highest possible accuracy. An excellent agreement (standard deviation of the fitted energies from the *ab initio* energies 0.28 kcal/mole) with the quantum-mechanical calculations was reached with a potential consisting of four terms: 1) a 6-12 Lennard–Jones contribution, in which different parameters are used to describe the interactions of methyls with the ester oxygens and with the anionic oxygens; 2) a contribution with twofold periodicity, accounting for the anomeric effects connected to the interactions between the lone pair electrons and the polar bonds of phosphorus with the anionic oxygens; 3) a contribution with threefold periodicity, representing the usual bond-staggering term; and 4) a Coulombic contribution, arising from electrostatic interactions between partially charged atoms.

Key words: Dimethylphosphate, conformational analysis of ~

1. Introduction

In a recent series of papers [1–6], the problem of the conformational analysis of the sugar-phosphate-sugar (SPS) complex, the simplest repeating unit of poly-

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0040–5744/78/0050/0169/$02.20

nucleotide chains (see Fig. 1 of Ref. [3]), was tackled with *ab initio* quantum-mechanical methods. The energies associated to a large number of conformations, computed within the Hartree-Fock approximation, were described through an analytical potential composed of an ethane-like torsional term, and of a 6-12 Lennard–Jones term, accounting for the interactions between nonbonded atoms. The four oxygens of the phosphate group, called Ox, were assigned different attractive and repulsive parameters than the four oxygens of the ribose rings and the hydroxyl terminal groups. This potential reproduces the positions of the relative maxima and minima with fairly good accuracy, but fails to predict the intensity of most barriers with the desirable accuracy. This is particularly true for the rotations ω' and ω around the two P–Ox bonds, where the relative uncertainty is the highest among the five rotations taken into account (for ω', with an average barrier height of 2.7 kcal/mole, the standard deviation amounts to 1.97 kcal/mole, and for ω, with an average barrier height of 1.8 kcal/mole, the standard deviation amounts to 1.30 kcal/mole). The small values of the barriers indicate that the constraints to rotation about the two P–Ox bonds are less strong than those about the other bonds of the chain, i.e., that ω'- and ω-rotations are the main source of flexibility for polynucleotides: a precise prediction of these barriers is thus an essential requirement for a valuable analysis of the conformations in polynucleotide chains. A way to improve the potential derived in Ref. [4] is a careful consideration of the results of the decomposition of the total *ab initio* energy in two-center contributions, made with Clementi's Bond Energy Analysis formalism [7]. Another approach, which may contribute to a deeper understanding of the origin of the torsional barriers, consists of the conformational study of simpler subsystems, chosen in such a way as to mimic the SPS molecule as closely as possible, but having a smaller number of internal degrees of freedom. The simplest subsystem representative of the phosphate group of polynucleotides is the dimethylphosphate anion (hereafter indicated as DMP^-): in this molecule, indeed, ω' and ω are the only internal degrees of freedom (when the two CH_3 groups are "frozen" in a certain position).

DMP^- was always taken as the model for the phosphate moiety of polynucleotides, both when applying classical potential functions [8] and when resorting to more or less sophisticated quantum-mechanical procedures [9–12].

However, the availability of *ab initio* results on the conformational energies of SPS allows us to make a more realistic forecast of the possibilities and the limitations of this choice. In SPS, the curves for the ω'- and ω-rotations are consistently different (Fig. 1 of Ref. [4]): in both cases the largest contribution to the nonbonded energy is given by Ox···H and Ox···C interactions; but, while in the latter case the closest contacts with Ox come from the methylene group $C_{5'}H_{7'}H_{8'}$, and only a small fraction of the barriers arises from nonbonded interactions, in the former the contacts come from the first ribose ring, and the interactions $C_2 \cdots Ox_{5'}$ and $H_4 \cdots Ox_{5'}$ account for the largest part of the strongest peak. So, even before doing any computation, it is reasonable to predict not only that DMP^- will be a better model for the ω- than for the ω'-barriers of SPS, but also that the ω'-barriers will be more fully simulated by a compound such as the ethyl methyl phosphate anion (EMP^-), in which the methyl of the ethyl group (with its carbon atom fixed at the same position of the C_2-atom in SPS, i.e. *gauche* to the first chain oxygen) plays a role similar to the first ribose ring of SPS when ω' is rotated. The study of EMP^- is in progress and will be described elsewhere. As regards DMP^-, we note that, in spite of the numerous investigations made on this molecule, no systematic study of the barriers to internal rotation was ever presented. Only recently Hayes *et al.* [13] published a paper on the conformational analysis of H_3PO_4, $H_2PO_4^-$ and HPO_4^{2-}, which may be regarded as a first step in this direction. They made use of the findings of Radom *et al.* [14], who had resorted to a Fourier series in order to separate out various physical effects on the mechanism of rotational barriers in simple molecules. In this paper, we endeavor to fill the gap, through the derivation of a "classical" potential function fitting a large body of quantum-mechanical computations; and, at the same time, to bring a contribution to the refinement of the description of the conformational behavior of polynucleotide chains, which is the main goal of our investigation.

2. Results of Quantum-Mechanical Computations

2.1. Geometrical Parameters

The fully extended conformation (planar zigzag disposition of the segment H_2–C_1–O_2–P–O_5–C_6–H_6, see Fig. 1) was taken as the starting point for measuring internal rotation angles (according to the convention adopted in Refs. [1–6], the *trans* conformation is assigned the value of 0°). Bond lengths and valence angles are such that DMP^- is super-imposable to the central part of the C(2′)-*endo* SPS complex represented in Fig. 1 of Ref. [3] (the two methyls are in an *eclipsed* arrangement). Our molecule does not possess the C_{2v} symmetry imposed in other cases [8, 9, 12] on the PO_4 moiety, so that the two rotations ω' and ω are not fully equivalent.

When varying the torsional angles, we held fixed both the bond lengths and the bond angles. Admittedly, a correct prediction of the ordering of conformational stabilities in a molecule is often impossible until a complete geometry optimization involving the bond distances, valence angles and torsional angles is considered. Had the primary goal of our work been the conformational study of DMP^- *per se*, the rigid rotator approximation would have been questionable; however, since we are essentially interested in gathering information suited to improve the description

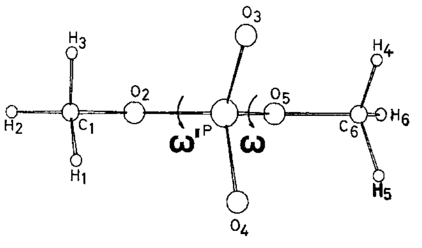

Fig. 1. View of DMP^- in the reference conformation ($\omega' = \omega = 0°$)

of the conformational preferences in polynucleotides, such assumption seems to us quite legitimate.

2.2. *Computational Procedure*

Ab initio computations were done with Clementi's IBMOL-6 program. We used a minimal basis set of Gaussian orbitals (see Tables 6–9 of Ref. [3] for orbital exponents and contraction coefficients), such that the 66 electrons of DMP^- (closed-shell configuration) were described with 142 primitive functions, contracted to 45: one ($1s$) for H, five ($1s$, $2s$, $2p_x$, $2p_y$, $2p_z$) for both C and O, and nine ($1s$, $2s$, $3s$, $2p_x$, $2p_y$, $2p_z$, $3p_x$, $3p_y$, $3p_z$) for P. This choice, made indispensable by our need of comparison with the previous results on SPS, might lead to an underestimation of some energy barriers, but should give results in qualitative agreement with those achieved with larger basis sets, as proved, e.g., by the comparison of the energies obtained without [9] and with [11] the inclusion of $3d$ orbitals on the P atom (the conformational preferences remain qualitatively the same in both cases, but in the latter the barriers are higher than in the former by a factor of ca. 1.2–1.5). In spite of the limitation of the basis set, the HOMO has a negative energy for all conformations: this ensures that our Hartree-Fock calculations minimize the energy (in singly negative ions, the Fock operator cannot have normalizable eigenfunctions when the HOMO energy is positive [15]).

2.3. *Conformational Energies*

The energies were computed for 86 conformations[1] corresponding to two pairs of values (0° and 105°) for both ω' and ω, plus a few further points in the (g^+, g^+) and (g^-, g^-) regions, that previous results [9, 12] had shown to be of low energy.

Our sampling of the conformational space, although large from the point of view of quantum-mechanical computations, is far from being sufficient to give a comprehensive idea of the overall shape of the three-dimensional energy surface. To do this, we shall derive an analytical expression, chosen in such a way as to reproduce *ab initio* results with the highest possible fidelity. Its use allows us to compute the energy associated to any conformation in a time smaller than that of an *ab initio* computation by several orders of magnitude, and thus, e.g., to have a sufficiently narrow grid at our disposal for drawing energy curves. A detailed discussion on the global energy surface is postponed after derivation of the potential. Here we just mention a few noteworthy features:

a) the lowest energy of our sampling is observed for $\omega' = 105°$, $\omega = 105°$, in agreement with all previous computations on DMP^-, that indicate the (g^+, g^+) region as the most stable one;
b) a second minimum, higher than the absolute minimum by 1.6 kcal/mole, is observed in the (g^-, g^-) region ($\omega' = 255°$, $\omega = 255°$);
c) the energy of the (t, t) conformation lies above the absolute minimum by 3.9

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[1] A list of these energies is available from the authors upon request.

kcal/mole, an amount very similar to that found by Gorenstein *et al.* [12] (3.4 kcal/mole), but smaller than that found by Newton [9] (ca. 7 kcal/mole).

The four conformational energy curves, of ω' at $\omega=0°$ (I) and $\omega=105°$ (III), and of ω at $\omega'=0°$ (II) and $\omega'=105°$ (IV) are shown in Fig. 2. The curve for the ω-rotation in DMP$^-$ is almost exactly superimposable to the corresponding curve in SPS (see Fig. 1 of Ref. [4]), while the curves for ω' are largely different in the two molecules, both in the peak heights and in the peak positions. As mentioned in the introductory section, this different behavior is expected: actually, in the case of the ω-rotation, the methylene group $C_{5'}H_{7'}H_{8'}$ of SPS keeps away the second ribose ring from the phosphate group, so that there are no contacts between the ribose ring and the phosphate closer than the closest contact between the methylene group and the phosphate; in the case of the ω'-rotation, on the contrary, the first ribose ring of SPS comes much closer to the phosphate than the methyl group does in DMP$^-$: as a consequence, an analytical expression constructed from the quantum-mechanical data on DMP$^-$ will be more reliably transferred to the ω- than to the ω'-rotation of SPS.

3. Derivation of a Classical Potential Function

Our previous experience on SPS had indicated three factors as possibly responsible for the energy variations associated with internal rotations: nonbonded interactions, torsional strains, and electrostatic interactions.

Let us first consider the nonbonded interactions. To begin with, we distinguish the two pendant oxygen atoms O_3 and O_4 from the two chain atoms O_2 and O_5: they will be denoted as OA and OE, respectively, where A stands for anionic and E for ester. This distinction is suggested by the results of the quantum-mechanical computations, that indicate, in these two classes of oxygen atoms, substantial differences (see Table 1) both of the net charges Q (computed according to Mulliken's Electron Population Analysis) and of the molecular orbital valency states MOVS (computed according to Clementi's Bond Energy Analysis).

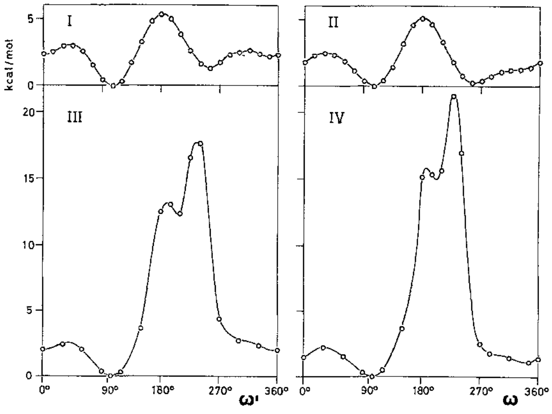

Fig. 2. *Ab initio* energies for the rotation of ω' at $\omega=0°$ (I), ω at $\omega'=0°$ (II), ω' at $\omega=105°$ (III) and ω at $\omega'=105°$ (IV)

Table 1. Net charge Q on, and molecular orbital valency state MOVS of the atoms of DMP$^-$, in the least-energy conformation (105°, 105°)

Atom	Q (a.u.)	MOVS (a.u.)
P	1.7268	1.94390
O_2	−0.6250	0.43725
C_1	−0.4117	1.20400
H_1	0.1598	0.26440
H_2	0.1577	0.27019
H_3	0.2003	0.28691
O_5	−0.6084	0.40929
O_3	−0.8521	0.31049
O_4	−0.8295	0.26965
C_6	−0.4196	1.19370
H_4	0.1579	0.25793
H_5	0.1829	0.27434
H_6	0.1608	0.27307

Secondly, we note that, of the 12 possible classes of interacting atoms (H···H, C···H, C···C, OA···H, OA···C, OA···OA, OE···H, OE···C, OE···OA, OE···OE, P···H, P···C), only 7 contribute to the energy barriers associated with ω'- and ω-rotations, namely H···H, C···H, C···C, OA···H, OA···C, OE···H and OE···C; interactions OA···OA, OE···OA and OE···OE are ruled out since the atoms of these pairs are at two-bond distance, and interactions P···H and P···C since P lies on the axis of both rotations. Of the "active" interactions, those of methyls with oxygen predominate over those between methyls in rotations I and II, while the opposite takes place in rotations III and IV, as is easily seen by examining how the interatomic distances vary with conformation. To avoid bias (due, e.g., to the under-estimation of barriers in our quantum-mechanical results) in the nonbonded energy parameters we shall derive, we exclude from our optimization all *ab initio* computations with energy higher than the global minimum by more than 10 kcal/mole. The exclusion should not imply any consequence from the thermodynamic point of view, since the Boltzmann factor causes the population of the excluded conformers to be quite negligible at room temperature. In the "allowed" regions, the shape of curves III and IV is similar to that of curves I and II. The nonbonded energy contribution, with the parameters obtained for SPS [4], accounts for only a part of the energy barriers, and it seems most unlikely that either the subdivision of Ox into OA and OE, or an enhancement of the repulsive character of some or all interactions will justify such barriers. So, their main origin should be found elsewhere. It is not too difficult to ascertain what form the function fitting *ab initio* data should have: the simplest expression complying with the requirements of being almost symmetrical about a maximum at 180°, of displaying two nearly equivalent minima at 105° and 255°, a secondary minimum near 0°, and two secondary maxima at ca. ±40° is

$$V_\alpha(\alpha) = \frac{V'}{2}(1 - \cos 3\alpha) + \frac{V''}{2}(1 + \cos 2\alpha) \tag{1}$$

where α is the dihedral angle (either ω' or ω) defining the molecular conformation: in other words, it is the superposition of a potential with twofold periodicity to the

Table 2. Parameters for the analytical potential in Eq. (2), before and after optimization

	Before optimization		After optimization	
	A[a]	$10^{-3}\cdot B$[b]	A[a]	$10^{-3}\cdot B$[b]
H···H	26.3	4.06	0.0	1.730
C···H	85.4	36.3	0.0	0.0
C···C	333	272	0.0	0.0
OA···H	360	12.8	630.0	11.90
OA···C	299	371	12.37	729.3
OE···H	360	12.8	276.5	50.97
OE···C	299	371	856.3	487.4
V'[c]		1.44		0.51
V''[c]		0.0		1.73
ε		∞[d]		1.00
K		−302.943		−280.427
Standard deviation[c]: for curve I (points 1 to 24)[e]		1.679		0.217
for curve II (points 1 and 25 to 47)[e]		1.265		0.308
for the 75 points used in optimization[f]		1.425		0.277

[a] $\mathrm{Kcal}\cdot\text{Å}^{6}\cdot\mathrm{mole}^{-1}$.

[b] $\mathrm{Kcal}\cdot\text{Å}^{12}\cdot\mathrm{mole}^{-1}$.

[c] Kcal/mole.

[d] The analytical potential used for SPS did not include the Coulombic term.

[e] Evaluated by means of the relation

$$\left\{\sum_{i=1}^{24}\{[B.E._{\alpha,i}-B.\ E._{\alpha,\mathrm{min}}]-[E_{\alpha,i}(\mathrm{calc})-E_{\alpha,\mathrm{min}}(\mathrm{calc})]\}^2/24\right\}^{1/2}$$

where $E_{\alpha,i}$ is the energy calculated with the analytical potential for the i'th conformation corresponding to the internal rotation angle α, $E_{\alpha,\mathrm{min}}(\mathrm{calc})$ is the lowest energy calculated for that rotation, and $B.\ E._{\alpha,i}$ and $B.\ E._{\alpha,\mathrm{min}}$ are the corresponding *ab initio* energies.

[f] Evaluated by means of the relation

$$\left\{\sum_{i=1}^{75}[B.\ E._i-E_i(\mathrm{calc})]^2/75\right\}^{1/2}$$

usual "bond-staggering" term with threefold periodicity. A truncated Fourier expansion like that in (1) was used by Hayes *et al.* [13] not only to describe the conformational energies of phosphoric acids, but also to analyse Newton's data [9] on DMP^-. The results of Ref. [13] prove that the twofold potential is essential in reproducing the conformational profiles by an analytical potential function. The physical effect reflected by this potential is the anomeric effect, i.e. the tendency for lone pairs of ester oxygens to be *gauche* relative to polar bonds: *gauche*-type conformations enhance the lone-pair back-donation to the electron withdrawing $P^{\delta+}-OA^{\delta-}$ bonds. In addition, the twofold potential, as given in (1), accounts for the interaction energy between lone pairs electrons on O_2 and O_5; in particular, it contributes a repulsive energy on the extended (t, t) conformation, thus re-

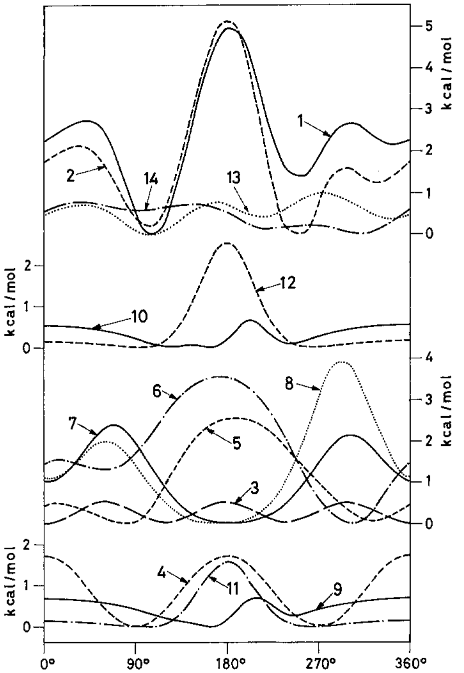

Fig. 3. Energy curves for the ω'-rotation (1) and for the ω-rotation (2), constructed with the analytical potential of Table 2, and decomposition of the energy into torsional (3), anomeric (4), nonbonded: OA···H, ω' (5); OA···H, ω (6); OA···C, ω' (7); OA···C, ω (8); OE···H, ω' (9); OE···H, ω (10); OE···C, ω' (11); OE···C, ω (12), and Coulombic components: ω' (13), ω (14)

moving one of the most disturbing deficiencies of classical potential functions, that invariably predict this structure as the most stable region.

On the basis of these considerations, we attempted to fit the following expression to *ab initio* binding energies:

$$E_{\text{calc}} = K + V_{\omega'}(\omega') + V_{\omega}(\omega) + \sum_{i>j} [V_{a,ij}(\omega', \omega) + V_{r,ij}(\omega', \omega) + V_{c,ij}(\omega', \omega)] \qquad (2)$$

where K is a constant including the interaction energies between a) directly bonded atoms, b) nonbonded atoms at two-bond distance, and c) nonbonded atoms belonging to P···H and P···C classes; $V_{\omega'}(\omega')$ and $V_{\omega}(\omega)$ are the contributions of the bond-staggering and the anomeric term defined by (1); $V_{a,ij}(\omega', \omega)$ is the attractive

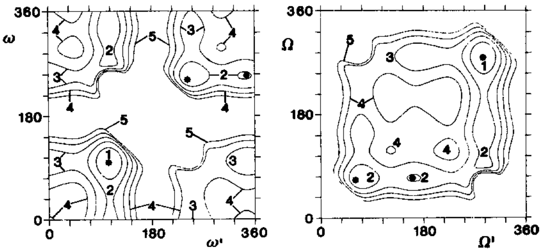

Fig. 4. Isoenergy contour map for the coupled rotation (ω', ω) in the *trans* convention (left) and in the *cis* convention (right). Energies are expressed in kcal/mole above the absolute minimum, which occurs at $\omega' = 105°$, $\omega = 100°$ ($\Omega' = 285°$, $\Omega = 280°$) and is indicated by a star. The other two stars indicate relative minima

part and $V_{r,ij}(\omega', \omega)$ is the repulsive part of the Lennard–Jones interaction between nonbonded atoms i and j at (more than two-bond) distance r_{ij} (Å): $V_{a,ij} = -A/r_{ij}^6$, $V_{b,ij} = B/r_{ij}^{12}$, and $V_{c,ij}(\omega', \omega) = 332.17 Q_i Q_j / \varepsilon r_{ij}$ is the Coulombic interaction between the same pairs of atoms.

We took, as a starting guess for the parameters of Eq. (2), the values obtained in Ref. [4] for SPS, and reproduced in the left part of Table 2. After optimization, made with a computer program including a subroutine, STEPIT, kindly provided by Prof. J. P. Chandler (Department of Computing and Information Sciences of the Oklahoma State University) through QCPE, the parameters take on the values reproduced in the right part of Table 2, and the standard deviation falls down to acceptably low values.

Figs. 3–5 show one-, two-, and three-dimensional plots of the conformational energy: Fig. 3 contains the curves for ω'- and ω-rotations as well as the decomposition of the energy into its components; Fig. 4 contains the isoenergy contour map for the simultaneous rotation of ω' and ω (presented, for the sake of an easier comparison with the literature, also in the *cis* convention in which our starting geometry corresponds to $\Omega' = \Omega = 180°$), and Fig. 5 contains a perspective view of the global energy surface. Both the properties of the potential function and the features of the DMP$^-$ conformational energy surface deserve a detailed discussion. The energy surface has a rather deep minimum at $\omega' = 105°$, $\omega = 100°$ and two secondary minima, of 1.13 kcal/mole at $\omega' = 250°$, $\omega = 250°$, and of 1.91 kcal/mole at $\omega' = 340°$, $\omega = 250°$. The (t, t) region corresponds to a local maximum (of 4.77 kcal/mole, at $\omega' = 300°$, $\omega = 40°$). Two further local maxima are observed at $\omega' = 45°$, $\omega = 295°$ (4.36 kcal/mole) and $\omega' = 300°$, $\omega = 300°$ (4.05 kcal/mole). Our map does not possess the four symmetry-equivalent regions (obtained by drawing the two diagonals from the corners of the squares of Fig. 4) that appear when using the simplified model with C_{2v} symmetry; nevertheless, the displacement from the symmetry is not too large, as evident in Fig. 5.

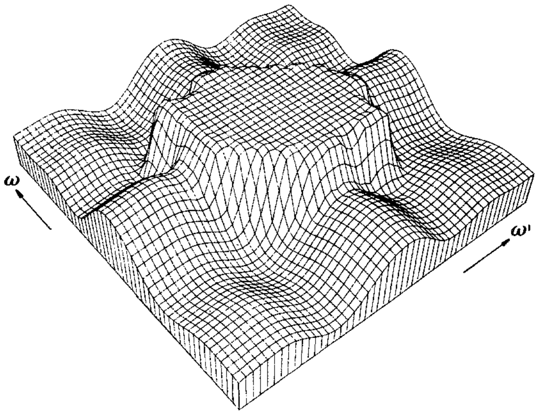

Fig. 5. Perspective view of the conformational energy surface of DMP$^-$. Energies higher than 10 kcal/mole above the global minimum were put equal to 10 kcal/mole

As regards the potential, we note that, in obtaining its final expression, no constraints were imposed to the parameters: in other words we performed what, in the preceding work on SPS, we called a "free" optimization [4], to distinguish it from the "guided" optimization, in which the starting parameters are allowed to vary only within a limited range, chosen in such a way as to save certain characteristics of the interactions (e.g., the occurrence of the strongest attraction in correspondence of an interatomic separation very close to the sum of the van der Waals radii of the interacting atoms). Since, as a general rule, the free optimization yields a higher numerical accuracy at the expense of the physical meaning of the parameters and of their transferability to different situations, one should be very careful when applying the present potential to molecules other than DMP^-. The optimized parameters give a clear evidence of three peculiar characteristics of the energetics involved in the rotations about bonds in the highly charged phosphate group: a) the preponderance of the anomeric (V'') over the bond-staggering (V') term, in line both with the predictions of Govil [16], who first introduced the anomeric term in the classical functions, correcting thus the error concerning the stability of the (t, t) conformation, and with the conclusions of Hayes *et al.* [13]; b) the much more attractive nature of the OA···H interaction (minimum of -8.34 kcal/mole at 1.83 Å) than of the OE···H interaction (minimum of -0.37 kcal/mole at 2.68 Å), and conversely of the OE···C interaction (almost purely repulsive) than of the OA···C interaction (minimum of -0.38 kcal/mole at 3.23 Å); c) the ability of the electrostatic term to account alone for the (attractive) C···H interaction and the (repulsive) C···C interaction.

4. Concluding Remarks

At the beginning of this paper, we remarked that the main purpose of our study on DMP^- was the derivation of a potential function capable of improving the analytical description of the intramolecular energy of SPS, especially for the ω-rotation, of which the corresponding rotation in DMP^- represents a good model. The present potential fulfils this condition: even neglecting the Coulombic contribution, whose trend is consistently different in the two molecules (cf. Fig. 3 of this paper and Fig. 3 of Ref. [4]), the standard deviation of analytical to *ab initio* energies for the 14 points of the ω-rotation decreases from 1.30 to 0.54 kcal/mole.

It is hoped that a good expression of the final potential for polynucleotides will be obtained by summarizing the conclusions reached for subsystems representative of the various internal rotations in SPS (like EMP^- for the ω'-rotation). The results described in the present paper encourage us to continue along this way.

Acknowledgement. G. L. is deeply grateful to the Direction of the "G. Donegani" Research Institute, and in particular to Prof. E. Clementi and his collaborators, for help during his stay there.

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Received March 6, 1978/June 26, 1978